METHOD OF TREATMENT

FIELD OF THE INVENTION

The present invention relates to methods for treating parasitic diseases using 4-amino-azepan-3-one protease inhibitors. In particular, the present methods serve to inhibit cysteine proteases of the papain superfamily. Thus, the present invention is useful for treating parasitic diseases which are mediated by the activity of such proteases. In particular, the present invention relates to treating malaria by inhibiting falcipain.

BACKGROUND OF THE INVENTION

Infection with *Plasmodium falciparum*, the most virulent human malaria pathogen, infects over 280 million people and is estimated to be responsible for over 1 million deaths annually (Gibbons, A. *Science* **1992**, *256*, 1135; Walsh, J. A. *Ann. N. Y. Acad. Sci.* **1989**, *569*, 1135). The *Plasmodium falciparum* parasite has a 48 hour life cycle within host erythrocytes that is responsible for all of the clinical manifestations of falciparum malaria. During this cycle, the erythrocyte is invaded by a merozoite, then the intracellular parasite develops from a ring stage into a more metabolically active trophozoite, divides asexually and becomes a schizont, and finally ruptures the host erythrocyte, releasing daughter merozoites that invade other erythrocytes to reinitiate the cycle. During the trophozoite stage, hemoglobin from the host erythrocyte is degraded for use as the parasites principal source of amino acids.

Rosenthal and coworkers have identified a 28 kD trophozoite cysteine protease (TCP or falcipain) from malaria parasites that mediates host hemoglobin degradation (Rosenthal, P. J.; McKerrow, J. H.; Aikawa, M.; Nagasawa, H.; Leech, J. H. *J. Clin. Invest.* **1988**, *82*, 1560) and is expressed only at the trophozoite stage (Rosenthal, P. J.; Kim, J. H.; McKerrow, J. H.; Leech, J. H. *J. Exp. Med.* **1987**, *166*, 816). Inhibition of this enzyme results in a blocking of hemoglobin degradation and killing of cultured parasites (Rosenthal, P. J.; Wollish, W. S.; Palmer, J. T.; Rasnick, D. *J. Clin. Invest.* **1991**, *88*, 1467; Li, R.; Kenyon, G. L.; Cohen, F. E.; Chen, X.; Gong, B.; Dominguez, J. N.; Davidson, E.; Kurzban, G.; Miller, R. E.; Nuzum, E. O.; Rosenthal, P. J.; McKerrow, J. H. *J. Med. Chem.* **1995**, *38*, 5031). In a mouse model of infection with *P. vinckei*, the analogous murine malarial parasite, treatment with cysteine protease inhibitors resulted in a long-term curative effect (>75 days) in 80% of animals (Rosenthal, P. J.; Lee, G. K.; Smith R. E. *J.*

Clin. Invest. **1993**, *91*, 1052). Thus, a selective inhibitor of falcipain may be an effective anti-malarial therapy either in conjunction with or as a replacement for the quinoline-derived drugs.

In addition to *Plasmodium falciparum*, other parasites utilize cysteine proteases in their life cycle. These include *Trypanosoma cruzi*, *Trypanosoma Brucei* [trypanosomiasis (African sleeping sickness, Chagas disease)], *Leishmania mexicana*, *Leishmania pifanoi*, *Leishmania major* (leishmaniasis), *Schistosoma mansoni* (schistosomiasis), *Onchocerca volvulus* [onchocerciasis (river blindness)] *Brugia pahangi*, *Entamoeba histolytica*, *Giardia lambia*, the helminths, *Haemonchus contortus* and *Fasciola hepatica*, as well as helminths of the genera *Spirometra*, *Trichinella*, *Necator* and *Ascaris*, and protozoa of the genera *Cryptosporidium*, *Eimeria*, *Toxoplasma* and *Naegleria* (McKerrow, J. H. (1995) in *Perspect. Drug Dis. Des.* **2**, eds., Craik, C. S., Debouck, C., pp. 437-444; Robertson, C. D., Coombs, G. H., North, M. J., Mottram, J. C. (1996) in *Perspect. Drug Dis. Des.* **6**, eds., McKerrow, J. H. and James, M. N. G., pp. 99-118).

It has now been discovered that certain 4-amino-azepan-3-ones are protease inhibitors, most particularly inhibitors of falcipain, and that these compounds are useful for treating parasitic diseases, particularly malaria.

Summary of the Invention

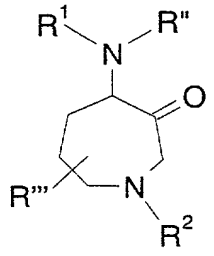
An object of the present invention is to provide methods of treatment which serve to inhibit cysteine proteases, and particularly cysteine proteases of the papain superfamily. The present methods are useful for treating parasitic diseases which may be therapeutically modified by altering the activity of such proteases. In particular, the present invention relates to treating malaria by inhibiting falcipain.

Accordingly, in the first aspect, this invention provides a method of treating parasitic diseases in which the disease pathology may be therapeutically modified by inhibiting proteases, such as cysteine proteases, using 4-amino-azepan-3-ones of Formula I.

In particular, these compounds are used in the present method to treat parasitic diseases by inhibiting cysteine proteases of the papain superfamily. Most particularly, the present invention provides a method of treating malaria by the inhibition of falcipain with such compounds.

Detailed Description of the Invention

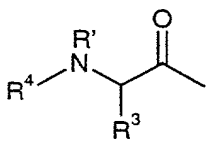
The present invention provides a method for treating parasitic diseases which may be therapeutically modified by altering the activity of cysteine proteases by administering to a patient in need thereof, particularly an animal, more particularly a mammal, most particularly a human being, one or more compounds of Formula I:



I

wherein:

R^1 is selected from the group consisting of: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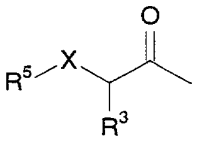
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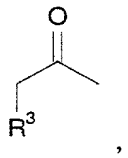
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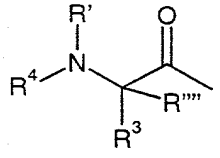
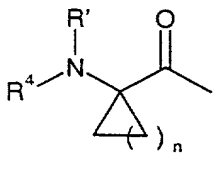
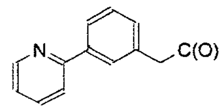
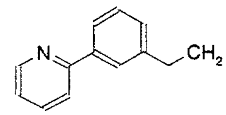
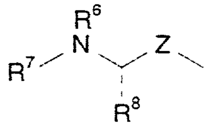

, and

;

R^2 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^9C(O)$-, $R^9C(S)$-, R^9SO_2-, $R^9OC(O)$-,

$R^9R^{11}NC(O)$-, $R^9R^{11}NC(S)$-, $R^9(R^{11})NSO_2$- 

, 



, and $R^9SO_2R^{11}NC(O)$-;

R^3 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl and ArC_{0-6}alkyl;

R^3 and R' may be connected to form a pyrrolidine, piperidine or morpholine ring;

R^4 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R^{12}NC(O)$-, and $R^5R^{12}NC(S)$-;

R^5 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^6 is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^7 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^{10}C(O)$-, $R^{10}C(S)$-, $R^{10}SO_2$-, $R^{10}OC(O)$-, $R^{10}R^{13}NC(O)$-, and $R^{10}R^{13}NC(S)$-;

R^8 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl and ArC_{0-6}alkyl;

R^9 is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{10} is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{11} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{12} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{13} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R' is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R" is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R"' is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

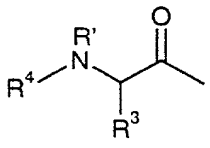
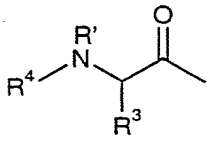
R"" is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl and ArC_{0-6}alkyl;

X is selected from the group consisting of: CH_2, S, and O;

Z is selected from the group consisting of: C(O) and CH_2;

n is an integer from 1 to 5;

and pharmaceutically acceptable salts, hydrates and solvates thereof.

R^1 is preferably  in compounds of Formula I. When R^1 is  :

R^3 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl,C_{2-6}alkenyl, C_{2-6}alkynyl, Het-C_{0-6}alkyl and Ar-C_{0-6}alkyl;

R^3 is preferably selected from the group consisting of: H, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, and C_{1-6}alkyl;

R^3 is more preferably selected from the group consisting of:

H, methyl, ethyl, n-propyl, prop-2-yl, n-butyl, isobutyl, but-2-yl, cyclopropylmethyl, cyclohexylmethyl, 2-methanesulfinyl-ethyl, 1-hydroxyethyl, toluyl, naphthalen-2-ylmethyl, benzyloxymethyl, and hydroxymethyl.

R^3 is even more preferably selected from the group consisting of: toluyl, isobutyl and cyclohexylmethyl.

R^3 is most preferably isobutyl.

R^4 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-

C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R^{13}NC(O)$-, and $R^5R^{13}NC(S)$-.

R^4 is preferably selected from the group consisting of: $R^5OC(O)$-, $R^5C(O)$- and R^5SO_2-.

R^4 is most preferably $R^5C(O)$-.

In some embodiments, R^4 is preferably methanesulfonyl.

R^5 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl or Het-C_{0-6}alkyl.

Preferably R^5 is selected from the group consisting of: C_{1-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl.

More preferably, and especially when R^4 is $R^5C(O)$-, R^5 is selected from the group consisting of:

methyl, especially halogenated methyl, more especially trifluoromethyl , especially C_{1-6}alkoxy substituted methyl, more especially phenoxy-methyl , 4-fluoro-phenoxy-methyl , especially heterocycle substituted methyl, more especially 2-thiophenyl-methyl ;

ethyl, especially piperidin-1-yl-ethyl;

butyl, especially aryl substituted butyl, more especially 4-(4-methoxy)phenyl-butyl;

isopentyl;

cyclohexyl;

pentanonyl, especially 4-pentanonyl;

butenyl, especially aryl substituted butenyl, more especially 4,4-bis(4-methoxyphenyl)-but-3-enyl;

acetyl;

phenyl, especially phenyl substituted with one or more halogens, more especially 3,4-dichlorophenyl and 4-fluorophenyl, especially phenyl substituted with one or more aryloxy or C_{1-6}alkoxy groups, more especially 3,4-dimethoxy-phenyl, 3-benzyloxy-4-methoxy-phenyl, especially phenyl substituted with one or more C_{1-6}alkyl sulfonyl groups, more especially 4-methanesulfonyl-phenyl;

benzyl;

naphthalenyl, especially naphthylen-2-yl;

benzo[1,3]dioxolyl, especially benzo[1,3]dioxol-5-yl;

furanyl, especially furan-2-yl, especially substituted furanyl, such as 5-nitro-furan-2-yl, 5-(4-nitrophenyl)-furan-2-yl, 5-(3-trifluoromethyl-phenyl)-furan-2-yl,more especially

halogen substituted furanyl, even more especially 5-bromo-furan-2-yl, more especially aryl substituted furanyl, even more especially 5-(4-chloro-phenyl)-furan-2-yl, more especially C_{1-6}alkyl substituted furanyl, even more especially 3-methyl-furan-2-yl, 4-methyl-furan-2-yl, 2,5-dimethyl-furan-2-yl, and 2,4-dimethyl-furan-3-yl;

tetrahydrofuranyl, tetrahydrofuran-2-yl;

benzofuranyl, especially benzofuran-2-yl, and substituted benzofuranyl, more especially 5-(2-piperazin-4-carboxylic acid *tert*-butyl ester- ethoxy) benzofuran-2-yl, 5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-yl, 5-(2-piperazin-1-yl-ethoxy)benzofuran-2-yl, 5-(2-cyclohexyl-ethoxy)-benzofuran-2-yl; especially C_{1-6}alkoxy substituted benzofuranyl, more especially 7-methoxy-benzofuran-2-yl, 5-methoxy-benzofuran-2-yl, 5,6-dimethoxy-benzofuran-2-yl, especially halogen substituted benzofuranyl, more especially 5-fluoro-benzofuran-2-yl, 5,6-difluoro-benzofuran-2-yl, especially C_{1-6}alkyl substituted benzofuranyl, most especially 3-methyl-benzofuran-2-yl, 3,5-dimethyl-benzofuran-2-yl, and 3-ethyl-benzofuran-2-yl; also 5-fluoro-3-methyl-benzofuran-2-yl, 6-fluoro-3-methyl-benzofuran-2-yl, 5-methoxy-3-methyl-benzofuran-2-yl, 4-methoxy-3-methyl-benzofuran-2-yl, and 6-methoxy-3-methyl-benzofuran-2-yl;

naphtho[2,1-b]-furanyl, especially naphtho[2,1-b]-furan-2-yl, alkyl substituted naphtho[2,1-b]-furanyl, especially 1-methyl-naphtho[2,1-b]-furan-2-yl;

benzo[*b*]thiophenyl, especially benzo[*b*]thiophen-2-yl; especially C_{1-6}alkoxy substituted benzo[*b*]thiophenyl, more especially 5,6-dimethoxy- benzo[*b*]thiophen-2-yl;

quinolinyl, especially quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-6-yl, and quinolin-8-yl;

quinoxalinyl, especially quinoxalin-2-yl;

1,8 naphthyridinyl, especially 1,8 naphthyridin-2-yl;

indolyl, especially indol-2-yl, especially indol-6-yl, indol-5-yl, especially C_{1-6}alkyl substituted indolyl, more especially N-methyl-indol-2-yl;

pyridinyl, especially pyridin-2-yl, pyridin-3-yl, pyridin-5-yl, especially C_{1-6}alkyl substituted pyridinyl, more especially 2-methyl-pyridin-5-yl, and oxy-pyridinyl, especially 1-oxy-pyridin-2-yland 1-oxy-pyridin-3-yl;;

furo[3,2-b]-pyridinyl, especially furo[3,2-b]-pyridin-2-yl, C_{1-6}alkyl substituted furo[3,2-b]-pyridinyl, especially 3-methyl-furo[3,2-b]-pyridin-2-yl;

thiophenyl, especially thiophen-3-yl, also thiophen-2-yl, especially C_{1-6}alkyl substituted thiophenyl, more especially 5-methyl-thiophen-2-yland 5-methyl-thiophen-3-yl, especially halogen substituted thiophenyl, more especially 4,5-dibromo-thiophen-2-yl;

thieno[3,2-*b*]thiophene, especially thieno[3,2-*b*]thiophene-2-yl, more especially C_{1-6}alkyl substituted thieno[3,2-*b*]thiophene-2-yl, more especially 5-*tert*-butyl-3-methyl-thieno[3,2-*b*]thiophene-2-yl;

isoxazolyl, especially isoxazol-4-yl, especially C_{1-6}alkyl substituted isoxazolyl, more especially 3,5-dimethyl- isoxazol-4-yl;

oxazolyl, especially oxazol-4-yl, more especially 5-methyl-2-phenyl oxazol-4-yl, 2-phenyl-5-trifluoromethyl-oxazol-4-yl; and

1H-benzoimidazolyl, especially 1H-benzoimidazol-5-yl.

When R^4 is R^5SO_2, R^5 is preferably pyridin-2-yl or 1-oxo-pyridin-2-yl.

R' is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl.

Preferably R' is selected from the group consisting of: H and naphthalen-2-yl-methyl.

Most preferably R' is H.

R" is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl.

Most preferably R" is H.

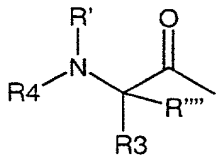
R'" is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, and Het-C_{0-6}alkyl.

R'" is preferably selected from the group consisting of: H and C_{1-6}alkyl.

R'" is more preferably selected from the group consisting of: H, methyl and 6,6-dimethyl.

When R'" is methyl, methyl is preferably selected from the group consisting of: 6-methyl and 7-methyl.

Even more preferably R'" is selected from the group consisting of: H, 6-methyl and 7-methyl, most preferably 7-methyl.

In compounds of Formula I, when R^1 is  :

R^3 is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, Het-C_{0-6}alkyl and Ar-C_{0-6}alkyl.

R^3 is preferably C_{1-6}alkyl.

R^3 is more preferably selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, isobutyl, t-butyl, cyclohexylmethyl, and toluyl.

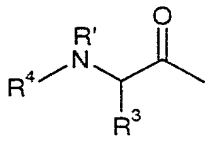
R"" is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl and ArC_{0-6}alkyl;

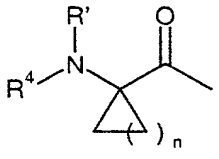
R"" is preferably C_{1-6}alkyl;

R"" is more preferably selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, isobutyl and t-butyl.

R"" is most preferably methyl.

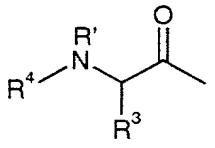
In such compounds, R', R", R"", R^4, and R^5 are as described above wherein

R^1 is  .

In compounds of Formula I, when R^1 is  :

n is preferably an integer of from 1 to 5; and

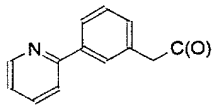
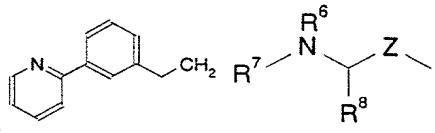
R', R", R"", R^4, and R^5 are as described above wherein

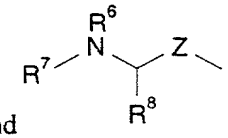
R^1 is  .

n is most preferably 3.

The ring may be unsubstituted or substituted with one or more of C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl, ArC_{0-6}alkyl, or halogen. The ring is preferably unsubstituted.

In compounds of Formula I, R^2 is selected from the group consisting of:

H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^9C(O)$-, $R^9C(S)$-, R^9SO_2-, $R^9OC(O)$-, $R^9R^{11}NC(O)$-, $R^9R^{11}NC(S)$-, $R^9R^{11}NSO_2$-,  ,  , and $R^9SO_2R^{11}NC(O)$-.

More preferably R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$-, R^9SO_2, $R^9R^{11}NC(O)$-, and  .

Even more preferably, R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$-, and R^9SO_2.

Most preferably R^2 is R^9SO_2.

In such embodiments:

R^6 is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl, preferably H.

R^7 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^{10}C(O)$-, $R^{10}C(S)$-, $R^{10}SO_2$-, $R^{10}OC(O)$-, $R^{10}R^{14}NC(O)$-, $R^{10}R^{14}NC(S)$-, R^7 is preferably $R^{10}OC(O)$.

R^8 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl and ArC_{0-6}alkyl; preferably C_{1-6}alkyl, more preferably isobutyl.

R^9 is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl.

R^9 is preferably selected from the group consisting of: C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl.

More preferably, R^9 is selected from the group consisting of:

methyl;

ethyl, especially C_{1-6}alkyl-substituted ethyl, more especially 2-cyclohexyl-ethyl;

propyl;

butyl, especially C_{1-6}butyl, more especially 3-methylbutyl;

tert-butyl, particularly when R^2 is $R^9OC(O)$;

isopentyl;

phenyl, especially halogen substituted phenyl, more especially 3,4-dichlorophenyl , 4-bromophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, especially C_{1-6}alkoxy phenyl, more especially 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, especially cyanophenyl, more especially 2-cyanophenyl; especially C_{1-6}alkyl substituted phenyl, more especially 4-ethyl-phenyl, 2-methyl phenyl, 4-methyl phenyl, especially C_{1-6}alkyl sulfonyl substituted phenyl, more especially 4-methanesulfonyl phenyl, and 2-methanesulfonyl phenyl;

toluyl, especially Het-substituted toluyl, more especially 3-(pyridin-2-yl)toluyl;

naphthylene, especially naphthyl-2-ene;

benzoic acid, especially 2-benzoic acid;

benzo[1,3]dioxolyl, especially benzo[1,3]dioxol-5-yl;

benzo[1,2,5]oxadiazolyl, especially benzo[1,2,5]oxadiazol-4-yl;

pyridinyl, especially pyridin-2-yl, pyridin-3-yl, especially 1-oxy-pyridinyl, more especially 1-oxy-pyridin-2-yl, 1-oxy-pyridin-3-yl; especially C_{1-6}alkylpyridinyl, more especially 3-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl;

thiophenyl, especially thiophenyl-2-yl;

thiazolyl, especially thiazol-2-yl;

1H-imidazolyl, especially 1H-imidazol-2-yl, 1H-imidazol-4-yl, more especially C_{1-6}alkyl substituted imidazolyl, even more especially 1-methyl-1H-imidazol-2-yl, 1-methyl-1H-imidazol-4-yl, and 1,2-dimethyl-1H-imidazol-4-yl;

triazolyl, especially 1H-[1,2,4]triazolyl, more especially 1H-[1,2,4]triazol-3-yl, especially C_{1-6}alkyl substituted 1H-[1,2,4]triazolyl, more especially 5-methyl-1H-[1,2,4]triazol-3-yl; and

isoxazolyl, especially isoxazol-4-yl, especially C_{1-6}alkyl substituted isoxazolyl, more especially 3,5-dimethyl- isoxazol-4-yl.

When R^2 is R^9SO_2, R^9 is most preferably selected from the group consisting of: pyridin-2-yl and 1-oxy-pyridin-2-yl.

When R^2 is $R^9SO_2R^{11}NC(O)$-, R^9 is preferably Ar-C_{0-6}alkyl, more preferably Ar, most preferably substituted phenyl such as 2-methyl phenyl, 4-methyl phenyl, 2-chloro phenyl, and 4-fluoro phenyl.

When R^2 is $R^9C(O)$-, R^9 is preferably selected from the group consisting of C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, and Het-C_{0-6}alkyl, more preferably 1-oxy-pyridin-2-yl, cyclohexyl ethyl, and 3-methyl butyl.

R^{11} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl.

When R^2 is $R^9SO_2R^{11}NC(O)$-, R^{11} is preferably H.

When R^2 is Ar-C_{0-6}alkyl, R^2 is preferably phenyl, especially substituted phenyl, more especially halogen substituted phenyl, even more especially 2-fluorobenzyl.

When R^2 is C_{1-6}alkyl, R^2 is preferably selected from 1-propyl, 1-butyl, and 1-pentyl.

When R^2 is Het-C_{0-6}alkyl, Het-C_{0-6}alkyl is preferably Het-methyl, and Het in Het-methyl is preferably selected from the group consisting of:

pyridinyl, especially pyridin-2-yl, especially C_{1-6}alkylpyridinyl, more especially 6-methyl-pyridin-2-yl;

thiophenyl, especially thiophene-2-yl, more especially thiophen-2-yl or benzo[b]thiophen-2-yl;

thiazolyl, especially thiazol-4-yl such as 1-(2-morpholin-4-yl-thiazol-4-yl), and 1-(isothiazol-3-yl);

1H-imidazolyl, especially 1H-imidazol-2-yl, 1H-imidazol-4-yl, especially C_{1-6}alkyl substituted imidazolyl, more especially 1-methyl-1H-imidazol-2yl;

triazolyl, especially 3H-[1,2,3]triazolyl, more especially 3H-[1,2,3]triazol-4-yl, especially C_{1-6}alkyl substituted 3H-[1,2,3]triazolyl, more especially 3-phenyl-3H-[1,2,3]triazolyl -4-yl;

quinolinyl, especially quinolin-2-yl, quinolin-2-yl;

furanyl, especially furan-2-yl, especially substituted furanyl, such as 5-ethyl-furan-2-yl;

thieno[3,2-b]thiophene, especially thieno[3,2-b]thiophene-2-yl, especially C_{1-6}alkyl substituted thieno[3,2-b]thiophenyl, especially 3,4-dimethyl-thieno[3,2-b]thiophene-2-yl.

R^2 is also preferably:

H;

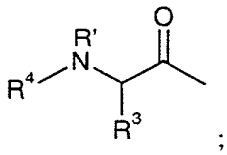
toluyl;

aryl substituted ethyl, especially 2-phenyl ethyl, 2-[3-(pyridin-2-yl) phenyl] ethyl.

Compounds of Formula I where R" and R"' are both H are preferred. Also preferred are such compounds wherein R"' is selected from the group consisting of: 6-methyl and 7-methyl, preferably 7-methyl.

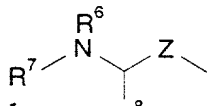
More preferred are compounds of Formula I wherein:

R^1 is



;

R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$-, R^9SO_2,



$R^9R^{11}NC(O)$-, and ;

R^3 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl and Ar-C_{0-6}alkyl;

R^4 is selected from the group consisting of: $R^5OC(O)$-, $R^5C(O)$- and R^5SO_2-;

$R^5$is selected from the group consisting of: C_{1-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^6 is H;

R^7 is $R^{10}OC(O)$;

R^8 is C_{1-6}alkyl;

R^9 is selected from the group consisting of: C_{1-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{10} is selected from the group consisting of: C_{1-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R' is H;

R" is H;

R"' is H; and

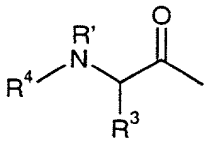
Z is selected from the group consisting of: C(O) and CH_2.

Also preferred are such compounds wherein R"' is selected from the group consisting of: 6-methyl and 7-methyl, preferably 7-methyl.

Even more preferred are such compounds of Formula I wherein R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$-, R^9SO_2.

Yet more preferred are compounds of Formula I wherein:

R^1 is



;

R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$- and R^9SO_2;

R^3 is selected from the group consisting of: H, methyl, ethyl, n-propyl, prop-2-yl, n-butyl, isobutyl, but-2-yl, cyclopropylmethyl, cyclohexylmethyl, 2-methanesulfinyl-ethyl, 1-hydroxyethyl, toluyl, naphthalen-2-ylmethyl, benzyloxymethyl, and hydroxymethyl;

R^4 is $R^5C(O)$-;

R^5 is selected from the group consisting of:

methyl, especially halogenated methyl, more especially trifluoromethyl , especially C_{1-6}alkoxy substituted methyl, more especially phenoxy-methyl , 4-fluoro-phenoxy-methyl , especially heterocycle substituted methyl, more especially 2-thiophenyl-methyl ;

ethyl, especially piperidin-1-yl-ethyl;

butyl, especially aryl substituted butyl, more especially 4-(4-methoxy)phenyl-butyl;

isopentyl;

cyclohexyl;

pentanonyl, especially 4-pentanonyl;

butenyl, especially aryl substituted butenyl, more especially 4,4-bis(4-methoxyphenyl)-but-3-enyl;

acetyl;

phenyl, especially phenyl substituted with one or more halogens, more especially 3,4-dichlorophenyl and 4-fluorophenyl, especially phenyl substituted with one or more aryloxy or C_{1-6}alkoxy groups, more especially 3,4-dimethoxy-phenyl, 3-benzyloxy-4-methoxy-phenyl, especially phenyl substituted with one or more C_{1-6}alkyl sulfonyl groups, more especially 4-methanesulfonyl-phenyl;

benzyl;

naphthalenyl, especially naphthylen-2-yl;

benzo[1,3]dioxolyl, especially benzo[1,3]dioxol-5-yl;

furanyl, especially furan-2-yl, especially substituted furanyl, such as 5-nitro-furan-2-yl, 5-(4-nitrophenyl)-furan-2-yl, 5-(3-trifluoromethyl-phenyl)-furan-2-yl,more especially halogen substituted furanyl, even more especially 5-bromo-furan-2-yl, more especially aryl substituted furanyl, even more especially 5-(4-chloro-phenyl)-furan-2-yl, more especially

C_{1-6}alkyl substituted furanyl, even more especially 3-methyl-furan-2-yl, 4-methyl-furan-2-yl, 2,5-dimethyl-furan-2-yl, and 2,4-dimethyl-furan-3-yl;

tetrahydrofuranyl, especially tetrahydrofuran-2-yl;

benzofuranyl, especially benzofuran-2-yl, and substituted benzofuranyl, more especially 5-(2-piperazin-4-carboxylic acid *tert*-butyl ester- ethoxy) benzofuran-2-yl, 5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-yl, 5-(2-piperazin-1-yl-ethoxy)benzofuran-2-yl, 5-(2-cyclohexyl-ethoxy)-benzofuran-2-yl; especially C_{1-6}alkoxy substituted benzofuranyl, more especially 7-methoxy-benzofuran-2-yl, 5-methoxy-benzofuran-2-yl, 5,6-dimethoxy-benzofuran-2-yl, especially halogen substituted benzofuranyl, more especially 5-fluoro-benzofuran-2-yl, 5,6-difluoro-benzofuran-2-yl, especially C_{1-6}alkyl substituted benzofuranyl, most especially 3-methyl-benzofuran-2-yl, 3,5-dimethyl-benzofuran-2-yl, and 3-ethyl-benzofuran-2-yl; also 5-fluoro-3-methyl-benzofuran-2-yl, 6-fluoro-3-methyl-benzofuran-2-yl, 5-methoxy-3-methyl-benzofuran-2-yl, 4-methoxy-3-methyl-benzofuran-2-yl, and 6-methoxy-3-methyl-benzofuran-2-yl;

naphtho[2,1-b]-furanyl, especially naphtho[2,1-b]-furan-2-yl, alkyl substituted naphtho[2,1-b]-furanyl, especially 1-methyl-naphtho[2,1-b]-furan-2-yl;

benzo[*b*]thiophenyl, especially benzo[*b*]thiophen-2-yl; especially C_{1-6}alkoxy substituted benzo[*b*]thiophenyl, more especially 5,6-dimethoxy- benzo[*b*]thiophen-2-yl;

quinolinyl, especially quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-6-yl, and quinolin-8-yl;

quinoxalinyl, especially quinoxalin-2-yl;

1,8 naphthyridinyl, especially 1,8 naphthyridin-2-yl;

indolyl, especially indol-2-yl, especially indol-6-yl, indol-5-yl, especially C_{1-6}alkyl substituted indolyl, more especially N-methyl-indol-2-yl;

pyridinyl, especially pyridin-2-yl, pyridin-3-yl, pyridin-5-yl, especially C_{1-6}alkyl substituted pyridinyl, more especially 2-methyl-pyridin-5-yl, and oxy-pyridinyl, especially 1-oxy-pyridin-2-yland 1-oxy-pyridin-3-yl;;

furo[3,2-b]-pyridinyl, especially furo[3.2-b]-pyridin-2-yl, C_{1-6}alkyl substituted furo[3,2-b]-pyridinyl, especially 3-methyl-furo[3,2-b]-pyridin-2-yl;

thiophenyl, especially thiophen-3-yl, also thiophen-2-yl, especially C_{1-6}alkyl substituted thiophenyl, more especially 5-methyl-thiophen-2-yland 5-methyl-thiophen-3-yl, especially halogen substituted thiophenyl, more especially 4,5-dibromo-thiophen-2-yl;

thieno[3,2-*b*]thiophene, especially thieno[3,2-*b*]thiophene-2-yl, more especially C_{1-6}alkyl substituted thieno[3,2-*b*]thiophene-2-yl, more especially 5-*tert*-butyl-3-methyl-thieno[3,2-*b*]thiophene-2-yl;

isoxazolyl, especially isoxazol-4-yl, especially C_{1-6}alkyl substituted isoxazolyl, more especially 3,5-dimethyl- isoxazol-4-yl;

oxazolyl, especially oxazol-4-yl, more especially 5-methyl-2-phenyl oxazol-4-yl, 2-phenyl-5-trifluoromethyl-oxazol-4-yl; and

1H-benzoimidazolyl, especially 1H-benzoimidazol-5-yl.

R^9 is selected from the group consisting of:

methyl;

ethyl, especially C_{1-6}alkyl-substituted ethyl, more especially 2-cyclohexyl-ethyl;

propyl;

butyl, especially C_{1-6}butyl, more especially 3-methylbutyl;

tert-butyl, particularly when R^2 is $R^9OC(O)$;

isopentyl;

phenyl, especially halogen substituted phenyl, more especially 3,4-dichlorophenyl , 4-bromophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, especially C_{1-6}alkoxy phenyl, more especially 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, especially cyanophenyl, more especially 2-cyanophenyl; especially C_{1-6}alkyl substituted phenyl, more especially 4-ethyl-phenyl, 2-methyl phenyl, 4-methyl phenyl, especially C_{1-6}alkyl sulfonyl substituted phenyl, more especially 4-methanesulfonyl phenyl, and 2-methanesulfonyl phenyl;

toluyl, especially Het-substituted toluyl, more especially 3-(pyridin-2-yl)toluyl;

naphthylene, especially naphthyl-2-ene;

benzoic acid, especially 2-benzoic acid;

benzo[1,3]dioxolyl, especially benzo[1,3]dioxol-5-yl;

benzo[1,2,5]oxadiazolyl, especially benzo[1,2,5]oxadiazol-4-yl;

pyridinyl, especially pyridin-2-yl, pyridin-3-yl, especially 1-oxy-pyridinyl, more especially 1-oxy-pyridin-2-yl, 1-oxy-pyridin-3-yl; especially C_{1-6}alkylpyridinyl, more especially 3-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl;

thiophenyl, especially thiophenyl-2-yl;

thiazolyl, especially thiazol-2-yl;

1H-imidazolyl, especially 1H-imidazol-2-yl, 1H-imidazol-4-yl, more especially C_{1-6}alkyl substituted imidazolyl, even more especially 1-methyl-1H-imidazol-2-yl, 1-methyl-1H-imidazol-4-yl, and 1,2-dimethyl-1H-imidazol-4-yl;

triazolyl, especially 1H-[1,2,4]triazolyl, more especially 1H-[1,2,4]triazol-3-yl, especially C_{1-6}alkyl substituted 1H-[1,2,4]triazolyl, more especially 5-methyl-1H-[1,2,4]triazol-3-yl; and

isoxazolyl, especially isoxazol-4-yl, especially C_{1-6}alkyl substituted isoxazolyl, more especially 3,5-dimethyl- isoxazol-4-yl;

R' is H;

R" is H; and

R"' is H.

Also preferred are such compounds wherein R"' is selected from the group consisting of: 6-methyl and 7-methyl, preferably 7-methyl.

The following compounds are preferred for use in the present methods of treatment:

Chemical Name

Benzo[1,3]dioxole-5-carboxylic acid [(S)-1-(1-benzyl-3-oxoazepan-4-ylcarbamoyl)-3-methyl-butyl]amide;

Quinoline-2-carboxylic acid [(S)-1-(1-benzyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide;

5-(2-Morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid ((S)-3-methyl-1-{3-oxo-1-[2-(3-pyridin-2-yl-phenyl)acetyl]-azepan-4-ylcarbamoyl}-butyl)amide;

5-(2-Morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid ((S)-3-methyl-1-{3-oxo-1-[2-(3-pyridin-2-yl-phenyl)acetyl]-azepan-4-ylcarbamoyl}-butyl)amide;

4-((S)-4-Methyl-2-{[5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-carbonyl]amino}-pentanoylamino)-3-oxo-azepane-1-carboxylic acid phenylamide;

5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide;

5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide;

5-(2-Pyrrolidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide;

5-(2-Piperidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide;

Naphthlene-2-carboxylic acid ((S)-3-methyl-1-{3-oxo-1-[2-(3-pyridin-2-yl-phenyl)ethyl]-azepan-4-ylcarbamoyl}-butyl)amide;

1H-Indole-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide;

Benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide;

5-(2-Pyrrolidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide;

5-(2-Piperidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide;

5-(2-Morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(4-methyl-pentanoyl)-3-oxo-azepan-4-ylcarbamoyl]-buyl}-amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Naphthalene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-(2-Morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-(2-Morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-(2-Morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

4-[2-(2-{(S)-3-Methyl-1-[3-oxo-1-(pyidine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butylcarbamoyl}-benzofuran-5-yloxy)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester;

5-(2-Piperizin-1-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-butyl}-amide;

Quinoline-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Quinoline-6-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Quinoline-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Quinoline-3-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Isoquinoline-3-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Isoquinoline-1-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Quinoxaline-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

1H-Indole-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-Bromo-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-Nitro-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-(4-Nitro-phenyl)-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

(S)-2-[2-(4-Fluoro-phenoxy)-acetylamino]-4-methyl-pentanoic acid [3-oxo-(pyridine-2-sulfonyl)-azepan-4-yl]-amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5,6-Dimethoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-methyl-1H-imidazole-4-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(1-methyl-1H-imidazole-3-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(1H-imidazole-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(1-methyl-1H-imidazole-4-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

5-(4-Oxy-morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-Hydroxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(1-methyl-1H-imidazole-4-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)]-3-methyl-butyl}-amide;

Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-Bromo-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5,6-Dimethoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)]-3-methyl-butyl}-amide;

5-Bromo-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5,6-Dimethoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

1H-Indole-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzo[1,3]dioxole-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-(1-oxy-pyridine2-sulfonyl)-azepan-4-ylcarbamoyl]- -buty}-amide;

3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

1H-Indole-6-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzo[1,3]dioxole-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

3,4-Dihydro-2H-benzo[b][1,4]dioxepine-7-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]butyl}amide;

4,5-Dibromo-thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

1H-Indole-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-(4-Chloro-phenyl)-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzo[1,3]dioxole-5-carboxylic acid {(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3methyl-butyl}-amide;

5-Bromo-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

2-Phenyl-5-trifluoromethyl-oxazole-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzo[1,3]dioxole-5-carboxylic acid {(S)-1-[1-(4-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Benzofuran-2-carboxylic acid {(S)-1-[1-(4-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzo[1,3]dioxole-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

4-Fluoro-{(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-carbamoyl]-butyl}-benzamide;

3,4-Dihydro-2H-benzo[b][1,4]dioxepine-7-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]butyl}amide;

5-Methyl-thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

(S)-2-(3-Benzyl-ureido)-4-methyl-pentanoic acid [3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide;

5-Methoxy-benzofuran-2-carboxylic acid [(S)-1-(1-methanesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]-amide;

Furan-2-carboxylic acid ({(S)-1-[1-(4-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butylcarbamoyl}-methyl)-amide;

Quinoline-2-carboxylic acid {[(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

1-Methyl-1H-indole-2-carboxylic acid {[(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

5-Methoxy-benzofuran-2-carboxylic acid {[(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Quinoxaline-2-carboxylic acid {[(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid-{(S)-1-[1-(3-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

5-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(3-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-Methyl-benzofuran-2-carboxylic acid-{(S)-1-[1-(3-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Benzofuran-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

5-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

7-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-methylbenzofuran-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Benzo[b]thiophene-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Quinoxaline-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(2,2',4-tridueterio)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Quinoxaline-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-2-cyclohexyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

Benzofuran-2-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-pentyl}-amide;

Benzofuran-2-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide;

2-Phenyl-5-trifluoromethyl-oxazole-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5-Methyl-2-phenyl-oxazole-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

3,4-Dimethoxy-N-{(S)-1-[1-(4-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-benzamide;

Benzo[b]thiophene-2-carboxylic acid-{(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-yl carbamoyl]-3-methyl-butyl}-amide;

Benzofuran-2-carboxylic acid-{(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-yl carbamoyl]-3-methyl-butyl}-amide;

N-{(S)-1-[1-(4-Fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl}-3-methyl-butyl}-3,4-dimethoxy-benzamide;

Benzo[b]thiophene-2-carboxylic acid-{(S)-1-(1-methanesulfonyl-3-oxo-azepan-4-yl carbamoyl)-3-methyl-butyl]-amide;

Benzofuran-2-carboxylic acid-{(S)-1-(1-methanesulfonyl-3-oxo-azepan-4-yl carbamoyl)-3-methyl-butyl]-amide;

N-[(S)-1-(1-Methanesulfonyl)-3-oxo-azepan-4-ylcarbamoyl}-3-methyl-butyl}-3,4-dimethoxy-benzamide;

N-{(S)-1-[1-(2-Cyano-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl}-3-methyl-butyl}-4-methanesulfonyl-benzamide;

Benzofuran-2-carboxylic acid {(S)-1-[1-(2-cyano-benzenesulfonyl)- 3-oxo-azepan-4-yl carbamoyl]-3-methyl-butyl}-amide;

5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-(1-oxy-pyridine2-sulfonyl)-azepan-4-ylcarbamoyl]- -buty}-amide;

5-Methyl-2 –phenyl-oxazole-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

6-Methyl-N-{(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-nicotinamide;

5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

N-{(S)-1-[(1-(2-cyano-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl}-3-methyl-butyl}-3,4-dimethoxy-benzamide;

4-Methansulfonyl-N-{(S)-1-[4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-carbamoyl]-3-methyl-butyl-benzamide;

(S)-2-[5-(4-Methoxy-phenyl)-pentanoylamnio]-4-methyl-pentanoic acid [3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide;

(S)-2-[2-(3-Benzyloxy-4-methoxy-phenyl)-acetylamnio]-4-methylpentanoic acid [3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide;

5-Methoxybenzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

7-Methoxybenzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

3-Methylbenzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

1-Methyl-1H-indole-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Quinoxaline-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-1-[1-(4-chloro-benzenesulfonyl)- 3-oxo-azepan-4-yl carbamoyl]-3-methyl-butyl}-amide;

5-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(4-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

7-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(4-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-Methyl-benzofuran-2-carboxylic acid-{(S)-1-[1-(4-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Benzo[b]thiophene-2-carboxylic acid-{(S)-1-[1-(4-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Benzofuran-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

5-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

7-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-Methyl-benzofuran-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Benzo[b]thiophene-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

1-Methyl-1H-indole-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Benzofuran-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-Methoxy-benzofuran-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

7-Methoxy-benzofuran-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-Methyl-benzofuran-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Benzo[b]thiophene-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Quinoxaline-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

1-Methyl-1-H-indole-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5,6-Difluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

5,6-Difluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

Quinoline-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Quinoline-6-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Quinoline-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Isoquinoline-1-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Naphthalene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Quinoline-3-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

5,6-Dimethoxy-benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[1-(6-methyl-pyridine-2-sulfonyl)3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

(R)-1-Benzyl-5-oxo-pyrrolidine-2-carboxylic acid {(S)-3-methyl-1-{3-oxo-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)-ethyl]-amide;

Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[1-(3-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(3-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(3-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

5,6-Difluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide;

7-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(6-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

5,6-Dimethoxy-benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[1-(6-methyl-pyridine-2-sulfonyl)3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

5-Fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-Fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid{(S)-2-cyclohexyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

5,6-Dimethoxy-benzofuran-2-carboxylic acid{(S)-2-cyclohexyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(3-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(6-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Quinoline-8-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)-ethyl]-amide;

Naphthalene-1-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)-ethyl]-amide;

Quinoline-8-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide;

Naphthyridine-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Naphthalene-1-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(2-methyl-furan-3-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}-amide;

Quinoline-2-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7S)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Benzofuran-2-carboxylic acid {(S)-1-[-(3-fluoro-benzensulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-1-butyl}-amide;

Naphthalene-1-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Quinoline-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid ((S)-3-methyl-1-{3-oxo-1-[1-(1-oxy-pyridin-2-yl)-methanoyl]-azepan-4-ylcarbamoyl}-butyl)-amide;

Quinoline-8-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

Naphthalene-1-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

Quinoline-8-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide;

Naphthalene-1-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide;

5-Fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-Fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

6-Fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-Fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-Fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

6-Fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3,5-Dimethyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-Ethyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

4-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

6-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3,5-Dimethyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-Ethyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

4-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

4-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

1-methyl-naphtho[2,1-b]-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

6-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

Benzofuran-2-carboxylic acid [(S)-3-methyl-1-[3-oxo-1-quinolin-2-ylmethyl-azepan-4-ylcarbamoyl]-butyl}-amide;

3-Methyl-benzofuran-2-carboxylic acid [(S)-3-methyl-1-[3-oxo-1-quinolin-2-ylmethyl-azepan-4-ylcarbamoyl]-butyl}-amide;

Benzo[b]thiophene-2-carboxylic acid [(S)-3-methyl-1-[3-oxo-1-quinolin-2-ylmethyl-azepan-4-ylcarbamoyl]-butyl}-amide;

Benzo[b]thiophene-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-Methyl-benzofuran-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Quinoxaline-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

Quinoline-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

4-Methyl-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

5-Methoxy-benzofuran-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide; and

4-Methyl-furan-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide.

Specific representative compounds which are useful in the present methods are set forth in Examples 1-222.

The present invention includes deuterated analogs of the inventive compounds. A representative synthetic route for the deuterated compounds of the present invention is set forth in Scheme 7, below. The deuterated compounds of the present invention exhibit superior chiral stability compared to the protonated isomer.

Definitions

The compounds used in the present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds which release the active parent drug according to Formula I *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric

form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984).

"Proteases" are enzymes that catalyze the cleavage of amide bonds of peptides and proteins by nucleophilic substitution at the amide bond, ultimately resulting in hydrolysis. Such proteases include: cysteine proteases, serine proteases, aspartic proteases, and metalloproteases. The compounds of the present invention are capable of binding more strongly to the enzyme than the substrate and in general are not subject to cleavage after enzyme catalyzed attack by the nucleophile. They therefore competitively prevent proteases from recognizing and hydrolyzing natural substrates and thereby act as inhibitors.

The term "amino acid" as used herein refers to the D- or L- isomers of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

"C_{1-6}alkyl" as applied herein is meant to include substituted and unsubstituted methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl, pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. C_{1-6}alkyl may be optionally substituted by a moiety selected from the group consisting of: OR^{14}, $C(O)R^{14}$, SR^{14}, $S(O)R^{14}$, $NR^{14}{}_2$, $R^{14}NC(O)OR^5$, CO_2R^{14}, $CO_2NR^{14}{}_2$, $N(C{=}NH)NH_2$, Het, C_{3-6}cycloalkyl, and Ar; where R^5 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl; and R^{14} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

"C_{3-6}cycloalkyl" as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane and cyclohexane.

"C_{2-6} alkenyl" as applied herein means an alkyl group of 2 to 6 carbons wherein a carbon-carbon single bond is replaced by a carbon-carbon double bond. C_{2-6}alkenyl

includes ethylene, 1-propene, 2-propene, 1-butene, 2-butene, isobutene and the several isomeric pentenes and hexenes. Both cis and trans isomers are included.

"C_{2-6}alkynyl" means an alkyl group of 2 to 6 carbons wherein one carbon-carbon single bond is replaced by a carbon-carbon triple bond. C_{2-6} alkynyl includes acetylene, 1-propyne, 2-propyne, 1-butyne, 2-butyne, 3-butyne and the simple isomers of pentyne and hexyne.

"Halogen" means F, Cl, Br, and I.

"Ar" or "aryl" means phenyl or naphthyl, optionally substituted by one or more of Ph-C_{0-6}alkyl; Het-C_{0-6}alkyl; C_{1-6}alkoxy; Ph-C_{0-6}alkoxy; Het-C_{0-6}alkoxy; OH, $(CH_2)_{1-6}NR^{15}R^{16}$; $O(CH_2)_{1-6}NR^{15}R^{16}$; C_{1-6}alkyl, OR^{17}, $N(R^{17})_2$, SR^{17}, CF_3, NO_2, CN, CO_2R^{17}, $CON(R^{17})$, F, Cl, Br or I; where R^{15} and R^{16} are H, C_{1-6}alkyl, Ph-C_{0-6}alkyl, naphthyl-C_{0-6}alkyl or Het-C_{0-6}alkyl; and R^{17} is phenyl, naphthyl, or C_{1-6}alkyl.

As used herein "Het" or "heterocyclic" represents a stable 5- to 7-membered monocyclic, a stable 7- to 10-membered bicyclic, or a stable 11- to 18-membered tricyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure, and may optionally be substituted with one or two moieties selected from C_{0-6}Ar, C_{1-6}alkyl, OR^{17}, $N(R^{17})_2$, SR^{17}, CF_3, NO_2, CN, CO_2R^{17}, $CON(R^{17})$, F, Cl, Br and I, where R^{17} is phenyl, naphthyl, or C_{1-6}alkyl. Examples of such heterocycles include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridinyl, 1-oxo-pyridinyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, quinoxalinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furanyl, benzofuranyl, thiophenyl, benzo[b]thiophenyl, thieno[3,2-b]thiophenyl, benzo[1,3]dioxolyl, 1,8 naphthyridinyl, pyranyl, tetrahydrofuranyl, tetrahydropyranyl, thienyl, benzoxazolyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl, as well as triazolyl, thiadiazolyl, oxadiazolyl, isothiazolyl, imidazolyl, pyridazinyl, pyrimidinyl, triazinyl and tetrazinyl which are available by routine

chemical synthesis and are stable. The term heteroatom as applied herein refers to oxygen, nitrogen and sulfur.

Here and throughout this application the term C_0 denotes the absence of the substituent group immediately following; for instance, in the moiety ArC_{0-6}alkyl, when C is 0, the substituent is Ar, e.g., phenyl. Conversely, when the moiety ArC_{0-6}alkyl is identified as a specific aromatic group, e.g., phenyl, it is understood that the value of C is 0.

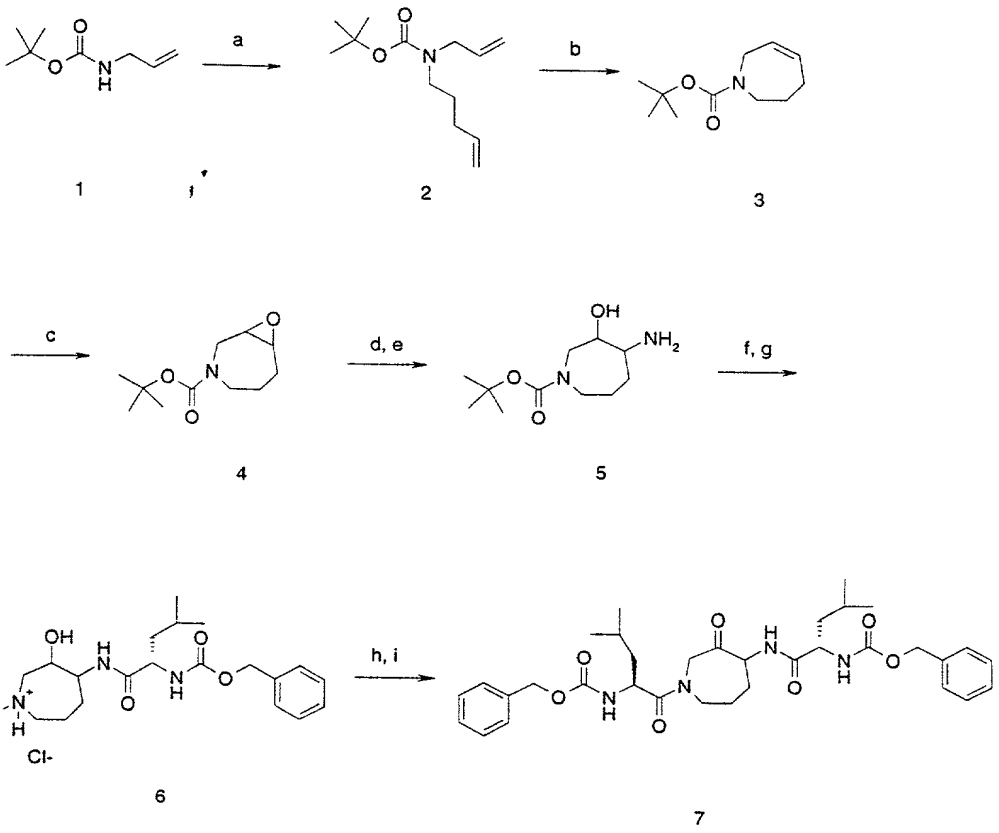
Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical.

Certain reagents are abbreviated herein. m-CPBA refers to 3-chloroperoxybenzoic acid, EDC refers to N-ethyl-N'(dimethylaminopropyl)-carbodiimide, DMF refers to dimethyl formamide, DMSO refers to dimethyl sulfoxide, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, and THF refers to tetrahydrofuran.

Methods of Preparation

Compounds of the general formula I may be prepared in a fashion analogous to that outlined in Schemes 1, 2 and 3. Alkylation of *tert*-butyl N-allylcarbamate (**1**) with a base such as sodium hydride and 5-bromo-1-pentene provides the diene **2**. Treatment of **2** with either 2,6-diisopropylphenylimido neophylidene molybenum bis(tert-butoxide) or bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride olefin metathesis catalysts developed by Grubbs provides the azepine **3**. Epoxidation of **3** with standard oxidizing agents common to the art such as *m*-CPBA provide the epoxide **4**. Nucleophilic epoxide ring opening may be effected with a reagent such as sodium azide to provide the azido alcohol (not shown) which may be reduced to the amino alcohol **5** under conditions common to the art such as 1,3-propanedithioln and triethylamine in methanol or with hydrogen gas in the presence of a catalyst such as palladium on carbon. Acylation of **5** with an acid such as Cbz-leucine in the presence of a coupling agent such as EDC followed by removal of the BOC protecting group under acidic conditions provides the amine salt **6**. Coupling of **6** with Cbz-leucine was effected with a coupling agent such as EDC provides the intermediate alcohol (not shown) which was oxidized with an oxidant such as pyridine sulfur trioxide complex in DMSO and triethylamine to provide the ketone **7**.

Scheme 1



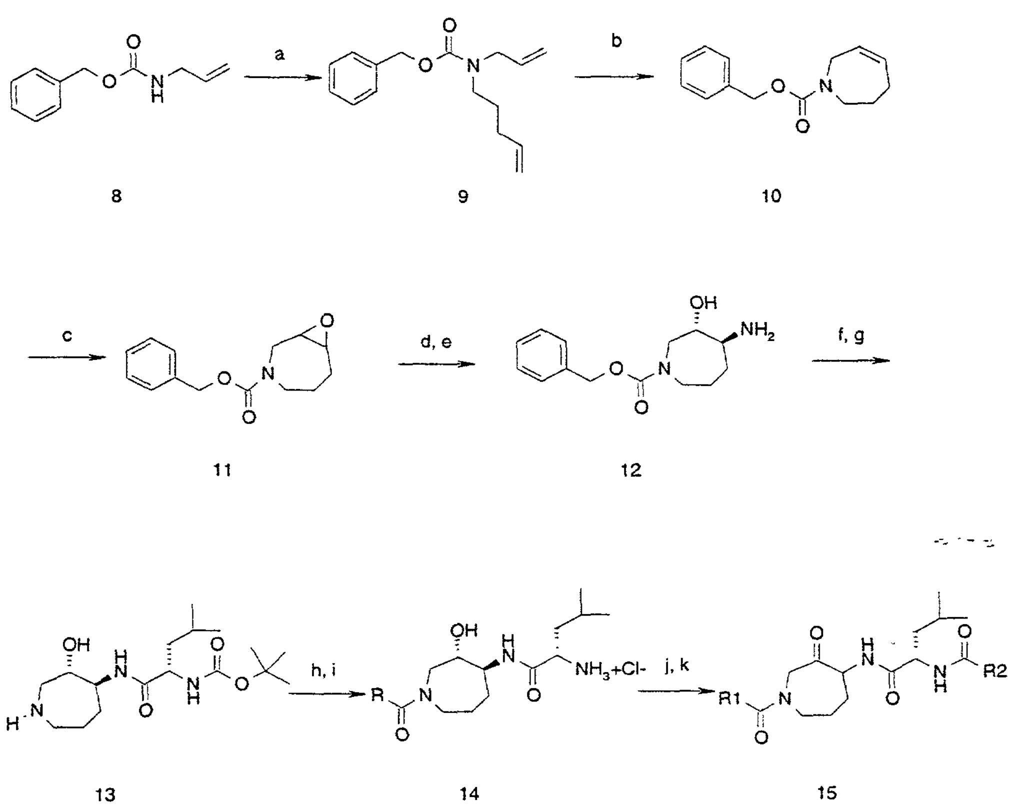
1 2 3 4 5 6 7

Reagents and conditions: a.) NaH, 5-bromo-1-pentene, DMF; b.) 2,6-diisopropylphenylimido neophylidene molybenum bis(tert-butoxide) or bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride catalyst, toluene c.) *m*-CPBA, CH_2Cl_2; d.) NaN_3, CH_3OH, H_2O, NH_4Cl; e.) 10% Pd/C, H_2, ; f.) Cbz-leucine, EDC, CH_2Cl_2; g.) HCl, EtOAc; h.) Cbz-leucine, EDC, CH_2Cl_2; i.) pyridine sulfur trioxide complex, DMSO, TEA.

Compounds of the general formula I wherein R1 and R2 are amides may be prepared in the general fashion outlined in Scheme 2. Alkylation of N-Cbz allyl amine (**8**) with a base such as sodium hydride and 5-bromo-1-pentene provides the diene **9**. Treatment of **9** with bis(tricyclohexylphosphine)benzylidine ruthenium(IV)dichloride olefin metathesis catalyst developed by Grubbs provides the azepine **10**. Epoxidation of **10** with standard oxidizing agents common to the art such as *m*-CPBA provide the epoxide **11**. Nucleophilic epoxide ring opening may be effected with a reagent such as sodium azide to provide the azido

alcohol (not shown) which may be reduced to the amino alcohol **12** with a reducing agent such as propanedithiol in the presence of triethylamine. Acylation of **12** with N-Boc-leucine and a coupling agent such as EDC followed by removal of the Cbz protecting group under hydrogenolysis conditions provides the amine **13**. Coupling of **13** with a carboxylic acid was effected with a coupling agent such as EDC followed by removal of the acid labile N-Boc protecting group with an acid such as HCl or TFA provides intermediate **14**. Acylation of **14** may be effected with a carboxylic acid in the presence of a coupling agent common to the art such as EDC to give the intermediate alcohol (not shown) which is oxidized with an oxidant such as pyridine sulfur trioxide complex in DMSO and triethylamine to provide the ketone **15**.

<u>**Scheme 2**</u>

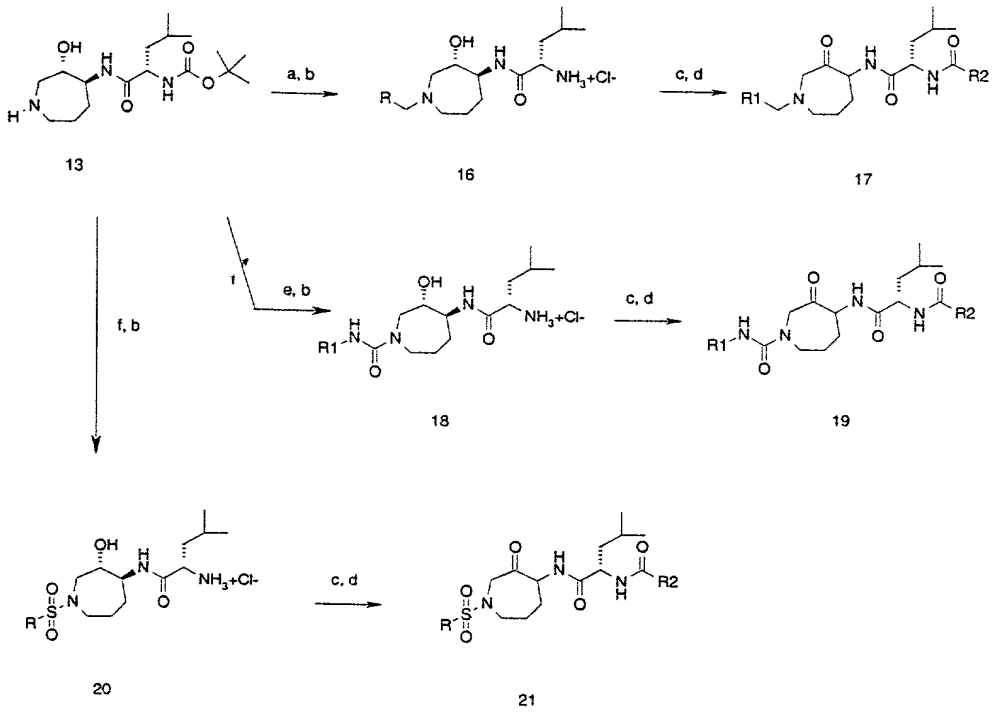


Reagents and conditions: a.) NaH, 5-bromo-1-pentene, DMF; b.) bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride catalyst, CH_2Cl_2; c.) *m*-CPBA, CH_2Cl_2; d.) NaN_3, CH_3OH, H_2O, NH_4Cl; e.) propanedithiol, CH_3OH, TEA; f.) Boc-leucine, EDC,

CH_2Cl_2; g.) 10% Pd/C, H_2; h.) R_1CO_2H, EDC, CH_2Cl_2 or R_1COCl, CH_2Cl_2; i.) HCl/ EtOAc; j.) R_2CO_2H, EDC, CH_2Cl_2; k.) pyridine sulfur trioxide complex, DMSO, TEA.

Compounds of the general formula I wherein R_2 is an alkyl, urea or sulphonamide group and R_1 is an amide may be prepared in the general fashion outlined in Scheme 3. Reductive amination of **13** may be effected by treatment with an aldehyde followed by a reducing agent such as sodium triacetoxyborohydride. Subsequent deprotection of the N-Boc group under acidic conditions provides the amine salt **16**. Coupling of **16** with an acid chloride or with a carboxylic acid in the presence of a coupling agent common to the art such as EDC followed by oxidation of the intermediate alcohol (not shown) with an oxidant such as pyridine sulfurtrioxide complex provides the ketone **17**. Alternatively, treatment of amine **13** with an isocyanate followed by deprotection of the N-Boc group provides the amine salt **18**. Acylation and oxidation provides the ketone **19**. Further derivatization of amine **13** may be effected by treatment with a sulphonyl chloride followed by deprotection of the N-Boc group to provide the amine salt **20**. Acylation and oxidation provides the ketone **21**.

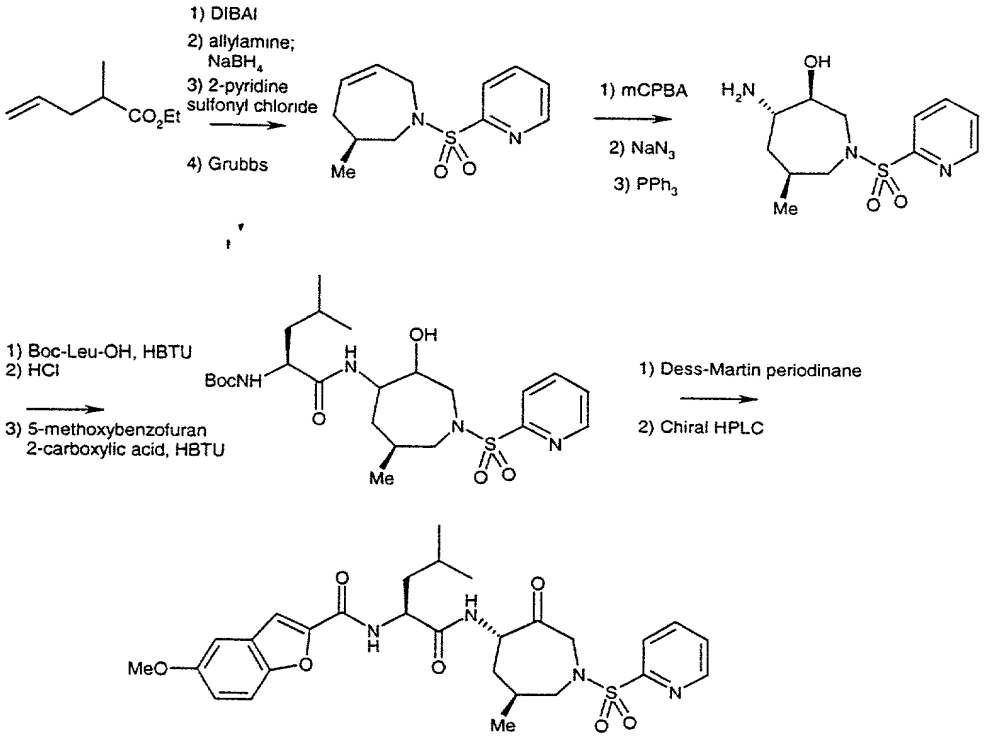
Scheme 3



Reagents and conditions: a.) R_1CHO, $NaBH(OAc)_3$; b.) HCl; c.) R_2CO_2H, EDC, CH_2Cl_2; d.) pyridine sulfurtrioxide complex, DMSO, TEA; e.) R_1NCO, base; f.) R_1SO_2Cl, TEA, CH_2Cl_2.

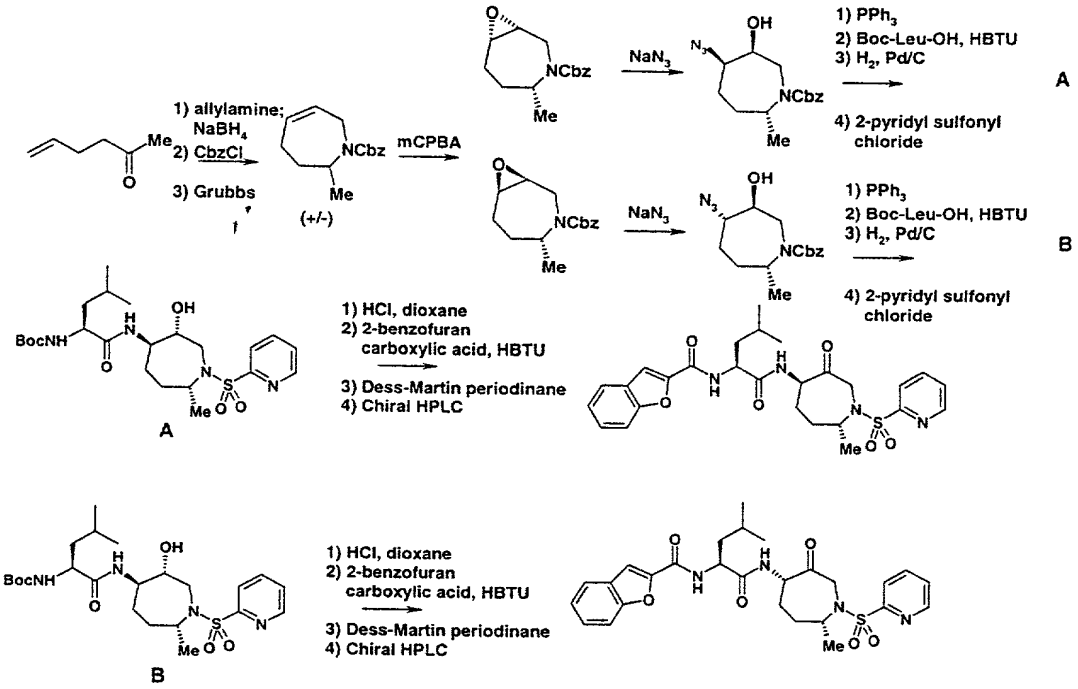
Compounds of the general formula I may be prepared in a fashion analogous to that outlined in Schemes 4, 5, 6, and 7

Scheme 4



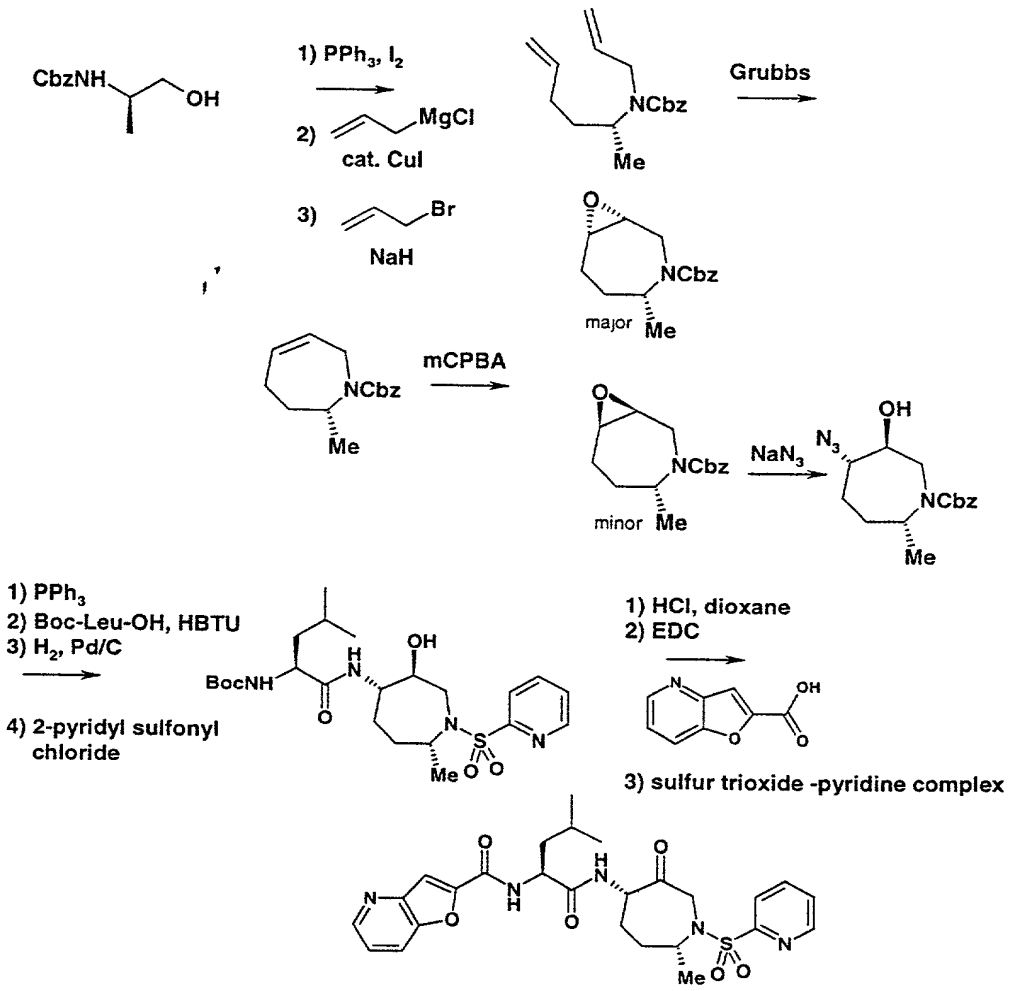
2-Methyl-pent-4-enoic acid ethyl ester is converted to a N-2-pyridinesulfonyl-azapine by reduction to the aldehyde, reductive amination with allylamine, sulfonylation with 2-pyridyl sulfonyl chloride, and olefin metathesis with Grubbs' catalyst. Epoxidation with mCPBA affords a mixture of epoxides that are separable by column chromatography. The syn epoxide is converted into an amino alcohol by opening with sodium azide followed by reduction with triphenylphosphine. Acylation of the free amine with Boc-leucine and a coupling reagent such as HBTU or EDC, followed by deprotection of the Boc group with HCl, and acylation with a variety of aromatic carboxylic acids and coupling reagents such as HBTU or EDC gives the intermediate alcohols. Final oxidation with Dess-Martin periodinane and HPLC affords the desired ketones.

Scheme 5



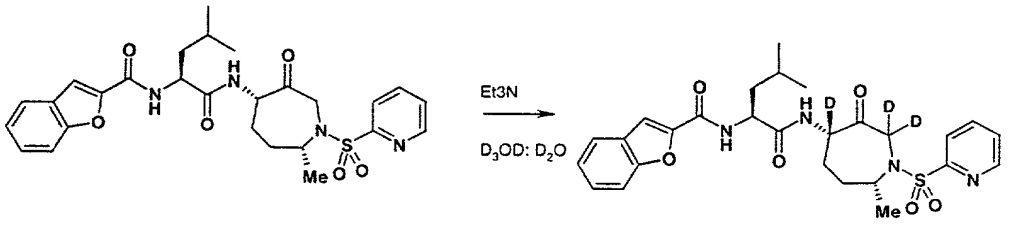
5-Hexen-2-one is converted to a N-carbobenzyloxy-azapine by reductive amination with allylamine, protection with carbobenzyloxychloride, and olefin metathesis with Grubbs' catalyst. Epoxidation with mCPBA affords a mixture of epoxides that are separable by column chromatography. Each epoxide is converted into an amino alcohol by opening with sodium azide followed by reduction with triphenylphosphine. Acylation of the free amine with Boc-leucine and a coupling reagent such as HBTU or EDC, followed by deprotection of the Cbz group by hydrogenolysis provides the secondary amines which are in turn sulfonylated with 2-pyridine sulfonylchloride. Deprotection of the Boc groups with HCl and acylation with a variety of aromatic carboxylic acids and coupling reagents such as HBTU or EDC gives the intermediate alcohols. Final oxidation with Dess-Martin periodinane and HPLC affords the desired ketones.

Scheme 6



Carbobenyzloxy-D-alaninol (Cbz-D-alaninol)is first converted to an iodide, then is reacted with allyl Grignard with a copper (I) catalyst or a similar allyl organometallic reagent. The amine is then alkylated with allyl iodide. Grubbs' catalyst is then used to form the azapine ring by ring closing metathesis. Epoxidation of the alkene followed by separation of the diastereomers followed by opening of the epoxide of the minor component with sodium azide provides the intermediate azido alcohol. Reduction of the azide followed by acylation of the amine with Boc-leucine followed by deprotection of the Cbz gives the intermediate secondary amine, which is then sulfonylated with an sulfonyl chloride. Deprotection of the Boc group followed by acylation and final oxidation of the secondary alcohol to the ketone provides the desired products.

Scheme 7



Deuterated inhibitors can be prepared from the parent inhibitors such as benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide by treating with a base such as triethyl amine and stirring for several days in a deteurated protic solvent such as CD_3OD: D_2O.

Utility of the Invention

In general, the present invention provides a method of inhibiting cysteine proteases of the papain superfamily by administering to a patient in need thereof, particularly an animal, more particularly a mammal, most particularly a human being, one or more of the compounds of Formula I.

The present invention also provides a method of treating a parasitic disease mediated by a cysteine protease by administering to a patient in need thereof, particularly an animal, more particularly a mammal, most particularly a human being, one or more of the compounds of Formula I.

Parasites known to utilize cysteine proteases in their life cycle include *Plasmodium falciparum* (malaria), *Trypanosoma cruzi*, *Trypanosoma Brucei* [trypanosomiasis (African sleeping sickness, Chagas disease)], *Leishmania mexicana*, *Leishmania pifanoi*, *Leishmania major* (leishmaniasis), *Schistosoma mansoni* (schistosomiasis), *Onchocerca volvulus* [onchocerciasis (river blindness)] *Brugia pahangi*, *Entamoeba histolytica*, *Giardia lambia*, the helminths, *Haemonchus contortus* and *Fasciola hepatica*, as well as helminths of the genera *Spirometra*, *Trichinella*, *Necator* and *Ascaris*, and protozoa of the genera *Cryptosporidium*, *Eimeria*, *Toxoplasma* and *Naegleria*. The present method provides treatment of diseases caused by infection by these parasites by inhibiting cysteine proteases of the papain superfamily by administering to a patient in need thereof, particularly an animal, more particularly a mammal, most particularly a human being, one or more of the compounds of Formula I.

As demonstrated in Table 1 beow, the compounds of Formula I used in the inventive method are especially effective in inhibition of one or more of the following parasitic proteases: falcipain (*P. falciparum*), cruzain (*T. cruzi*), rhodazain (*T. brucei rhodesiensi*), leishmania L (*Leishmania spp.*), leishmania B (*Leishmania spp.*), and schistosoma B (*S. mansoni*).

More particularly, the present invention provides a method of treating diseases selected from a group consisting of: malaria, trypanosomiasis (African sleeping sickness, Chagas disease), leishmaniasis, schistosomiasis, onchocerciasis (river blindness) and giardiasis by administering to a patient in need thereof, particularly an animal, more particularly a mammal, most particularly a human being, one or more of the compounds of Formula I.

Most particularly, the present invention provides a method of treating malaria, caused by infection with *Plasmodium falciparum,* by the inhibition of falcipain by administering to a patient in need thereof, particularly an animal, more particularly a mammal, most particularly a human being, one or more of the above-listed compounds.

The present method may be practiced by administering the above-listed compounds alone or in combination with other therapeutically effective compounds, including but not limited to quinoline-derived drugs.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical.

The present invention includes all esters, hydrates, solvates, complexes and prodrugs of the above-listed compounds useful in the inventive method. Prodrugs are any covalently bonded compounds which release the active parent drug *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric

form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The methods of treatment of this invention also use pharmaceutical compositions which comprise one or more of compounds of Formula I and a pharmaceutically acceptable carrier, diluent or excipient. Accordingly, the compounds of Formula I may be used in the manufacture of a medicament useful in the practice oof the present methods of treatment. Pharmaceutical compositions of compounds of Formula I prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water, or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride, or sodium citrate.

Alternately, these compounds may be encapsulated, tableted, or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly or filled into a soft gelatin capsule.

For rectal administration, the compounds of Formula I may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

In accordance with this invention, an effective amount of one or more compounds of Formula I is administered to inhibit the protease implicated with a particular condition or disease. Of course, this dosage amount will further be modified according to the type of administration of the compound. For example, for acute therapy, parenteral administration of an effective amount of a compound of Formula I is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit the parasitic protease, e.g. falcipain in the case of treatment of malaria. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of an inventive compound which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compound may be administered in the form of a prodrug which, in general, is designed to enhance absorption and is cleaved in vivo to form the active component. Efficacious levels may also be achieved by administration of pharmaceutically active metabolites or bioisosteres of the compound. Prodrugs of compounds of the present invention may be prepared by any suitable method.

The compounds used in this method may also be administered orally to the patient, in a manner such that the concentration of drug is sufficient to inhibit cysteine proteases, e.g. falcipain in the case of treatment of malaria, or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.1 to about 50 mg/kg given 1-2 times/day.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present method of treatment.

Biological Assays

The compounds used in the present method may be tested in one of several biological assays to determine the concentration of a compound which is required to have a given pharmacological effect. For example, an assay for determining parasitic cysteine protease catalytic activity and an assay to determine the amount of cysteine protease inhibition by a compound of the inventive method are provided.

Determination of cysteine protease catalytic activity

Standard assay conditions for the determination of kinetic constants used 10 uM fluorogenic peptide substrate, Cbz-Phe-Arg-AMC for the cysteine proteases from *Leishmania spp* and *Schistosoma Mansoni*, Cbz-Leu-Arg-AMC for the cysteine proteases from *Plasmodium falciparum* and *Trypanosoma brucei rhodesiensi*, and Ac-Lys-Glu-Lys-Leu-Arg-AMC (4 uM final substrate concentration) for the cysteine protease from *Trypoanosoma cruzi*, and were determined in 100 mM Na acetate at pH 5.5 containing 5 mM cysteine. Stock substrate solutions were prepared at concentrations of 10 mM in DMSO with 10 uM (4 uM for Ac-Lys-Glu-Lys-Leu-Arg-AMC) final substrate concentration in the assays. The final DMSO concentration was 2 % and the final volume was 100 uL. All assays were conducted at ambient temperature. Product progress curves were generated over 20 to 30 minutes following formation of AMC product.

Inhibition studies

Potential inhibitors were evaluated using the progress curve method. Assays were carried out in the presence of variable concentrations of test compound. Reactions were initiated by addition of enzyme to buffered solutions of inhibitor and substrate. Data analysis was conducted according to one of two procedures depending on the appearance of the progress curves in the presence of inhibitors. For those compounds whose progress curves were linear, apparent inhibition constants ($K_{i,app}$) were calculated according to equation 1 (Brandt *et al.*, *Biochemitsry*, **1989**, *28*, 140):

$$v = V_m A / [K_a(1 + I/K_{i,\,app}) + A] \qquad (1)$$

where v is the velocity of the reaction with maximal velocity V_m , A is the concentration of substrate with Michaelis constant of K_a, and I is the concentration of inhibitor.

For those compounds whose progress curves showed downward curvature characteristic of time-dependent inhibition, the data from individual sets was analyzed to give k_{obs} according to equation 2:

$$[AMC] = v_{ss}\, t + (v_0 - v_{ss})\,[1 - exp\,(-k_{obs}t)] / k_{obs} \qquad (2)$$

where [AMC] is the concentration of product formed over time t, v_0 is the initial reaction velocity and v_{ss} is the final steady state rate. Values for k_{obs} were then analyzed as a linear function of inhibitor concentration to generate an apparent second order rate constant (k_{obs} / inhibitor concentration or k_{obs} / [I]) describing the time-dependent inhibition. A complete discussion of this kinetic treatment has been fully described (Morrison *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **1988**, *61*, 201).

Exemplary inhibition data for the compounds used in the present method collected in accordance with the above-described procedure are listed in Table I.

The data in Table I demonstrate that the compounds of the present invention are efficacious inhibitors of the cysteine protease of one or more of the parasites selected from the group consisting of: *Leishmania spp*, *Schistosoma Mansoni*, *Plasmodium falciparum*, *Trypanosoma brucei rhodesiensi*, and *Trypoanosoma cruzi*, and thus, if administered according to the present method, may be therapeutically effective in treating malaria and other parasitic diseases identified herein above in animals, particularly mammals, most particularly human beings.

Examples

In the following synthetic examples, unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope.

Flash column chromatography was performed using silica gel 60 (Merck Art 9385). ^{1}H NMR (300 MHz) spectra were measured in $CDCl_3$ solutions and were determined on a

Varian 300 instrument utilizing a Varian UNITY*plus*300 operating software. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard, and coupling constants are given in Hertz. The following abbreviations are used for spin multiplicity: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, cm = complex multiplet. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer and are reported in wave numbers (cm-1).

Example 1

Preparation of benzo[1,3]dioxole-5-carboxylic acid [(S)-1-(1-benzyl-3-oxoazepan-4-ylcarbamoyl)-3-methyl-butyl]amide

a) allyl-pent-4-enyl-carbamic acid benzyl ester

To a suspension of NaH (1.83 g, 76.33 mmol of 90% NaH) in DMF was added benzyl allyl-carbamic acid benzyl ester (7.3 g, 38.2 mmol) in a dropwise fashion. The mixture was stirred at room temperature for approximately 10 minutes whereupon 5-bromo-1-pentene (6.78 mL, 57.24 mmol) was added in a dropwise fashion. The reaction was heated to 40°C for approximately 4 hours whereupon the reaction was partitioned between dichloromethane and water. The organic layer was washed with water (2x's), brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography of the residue (10% ethyl acetate:hexanes) provided 10.3 grams of the title compound as an oil. MS (ESI): 260 ($M+H^+$).

b) 2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester

To a solution of the compound of Example 1(a) (50 g) in dichloromethane was added bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride (5.0 g). The reaction was heated to reflux until complete as determined by TLC analysis. The reaction was concentrated *in vacuo*. Column chromatography of the residue (50% dichloromethane:hexanes) gave 35 g of the title compound. MS (ESI): 232 ($M+H^+$).

c) 8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester

To a solution of the compound of Example 1(b) (3.0 g, 13.0 mmol) in CH_2Cl_2 was added m-CPBA (6.7 g, 39.2 mmol). The mixture was stirred overnight at room temperature whereupon it was partitioned between CH_2Cl_2 and staurated K_2CO_3. The organic layer was

washed with sat. $NaHCO_3$, water, brine, dried ($MgSO_4$), filtered and concentrated to give 3.08 g of the title compound as an oil. MS (ESI): 248 ($M+H^+$), 270 ($M+Na^+$).

d) 4-azido-3-hydroxy-azepane-1-carboxylic acid benzyl ester

To a solution of the compound of Example 1(c) (2.0 g, 8.1 mmol) in methanol:water (8:1 solution) was added NH_4Cl (1.29 g, 24.3 mmol) and sodium azide (1.58 g, 24.30 mmol). The reaction was heated to 40°C until complete consumption of the starting epoxide was observed by TLC analysis. The majority of the solvent was removed *in vacuo* and the remaining solution was partitioned between ethyl acetate and pH 4 buffer. The organic layer was washed with sat. $NaHCO_3$, water, brine dried ($MgSO_4$), filtered and concentrated. Column chromatography (20% ethyl acetate:hexanes) of the residue provided 1.3 g of the title compound. MS (ESI): 291 ($M+H^+$) plus 0.14 g of trans-4-hydroxy-3-azido-hexahydro-1H-azepine

e) 4-amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester

To a solution of the azido alcohol of Example 1(d) (1.1 g, 3.79 mmol) in methanol was added triethylamine (1.5 mL, 11.37 mmol) and 1,3-propanedithiol (1.1 mL, 11.37 mL). The reaction was stirred until complete consumption of the starting material was observed by TLC analysis whereupon the reaction was concentrated *in vacuo*. Column chromatography of the residue (20% methanol:dichloromethane) provided 0.72 g of the title compound. MS (ESI): 265 ($M+H^+$).

f) 4-((S)-2-*tert*-butoxycarbonylamino-4-methyl-pentanoylamino)-3-hydroxy-azepan-1-carboxylic acid benzyl ester

To a solution of the amino alcohol of Example 1(e) (720 mg, 2.72 mmol) in CH_2Cl_2 was added EDC (521 mg), HOBt (368 mg) and N-Boc-leucine (630 mg). The reaction was maintained at room temperature until complete consumption of the starting material was observed by TLC analysis. The reaction was diluted with ethyl acetate and washed with 1N HCl, sat. K_2CO_3, water, brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography of the residue (3% methanol:dichloromethane) gave 1.0 g of the title compound. MS (ESI): 478 ($M+H^+$).

g) [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester

To a solution of the compound of Example 1(f) (1.0 g) and 10% Pd/C (catalytic) in ethyl acetate:methanol (2:1 solution) was affixed a balloon of hydrogen. The reaction was stirred until complete consumption of the starting material was observed by TLC analysis. The reaction was filtered to remove the catalyst and the filtrate was concentrated *in vacuo* to provide 0.82 g of the title compound. MS (ESI): 344 ($M+H^+$).

h) [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester

To a solution of the compound of Example 1(g) (0.69 g, 2.01 mmol) in CH_2Cl_2 was added benzaldehyde (0.32 mL, 3.01 mmol) followed by sodium triacetoxyborohydride (0.85 g, 4.02 mmol). The reaction was stirred until complete as determined by TLC analysis whereupon several drops of water were added to the reaction to destroy the excess sodium triacetoxyborohydride. The mixture was diluted with ethyl acetate washed with sat. $NaHCO_3$, water, brine, dried (Na_2SO_4), filtered and concentrated. Column chromatography of the residue (5% methanol:dichloromethane) gave 800 mg of the title compound. MS (ESI): 434 ($M+H^+$).

i) (S)-2-amino-4-methyl-pentanoic acid (1-benzyl-3-hydroxy-azepan-4-yl)-amide

To a solution of the compound of Example 1(h) (800 mg) in methanol (15 mL) was added 4M HCl in dioxane (15 mL). The reaction was stirred at room temperature overnight whereupon it was concentrated *in vacuo* to give 800 mg of the title compound. MS (ES): 334 (M+H+).

j) benzo[1,3]dioxole-5-carboxylic acid [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-amide

To a solution of the amine salt of Example 1(i) (200 mg, 0.49 mmol) in CH_2Cl_2 was added triethylamine (0.17 mL, 1.22 mmol), EDC (103.5 mg, 0.54 mmol), HOBt (73 mg, 0.54 mmol) and benzo[1,3]dioxole-5-carboxylic acid (90 mg, 0.54 mmol). The reaction was stirred until complete by TLC analysis. The reaction was diluted with ethyl acetate and washed with sat. $NaHCO_3$, water, brine, dried (Na_2SO_4), filtered and concentrated. Column chromatography of the residue (5% methanol:dichloromethane) gave 0.14 g of the title compound. MS (ESI): 482 ($M+H^+$).

k) benzo[1,3]dioxole-5-carboxylic acid [(S)-1-(1-benzyl-3-oxoazepan-4-ylcarbamoyl)-3-methyl-butyl]amide

To a solution of the alcohol of Example 1(j) (130 mg, 0.21 mmol) in DMSO was added TEA (0.17 mL) and pyridine sulfur trioxide complex (96 mg, 0.61 mmol). The reaction was stirred at room temperature for approximately 2 hours whereupon it was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography of the residue (5% CH_3OH:CH_2Cl_2) provided 100 mg of the title compound as a mixture of diastereomers. Separation of the diastereomers by HPLC (Whelk-O1; ethanol/hexanes) provided the title compound. MS (ESI): 480.3 ($M+H^+$).

Example 2

Preparation of Quinoline-2-carboxylic acid [(S)-1-(1-benzyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide

Following the procedure of Example 1(a)-1(k), except substituting quinoline-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 492.4 ($M+H^+$).

Example 3

Preparation of 5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid ((S)-3-methyl-1-{3-oxo-1-[2-(3-pyridin-2-yl-phenyl)acetyl]-azepan-4-ylcarbamoyl}-butyl)amide

a) methyl 3-(trifluoromethylsulfonyloxy)phenylacetate

To an oven-dried flask under argon atmosphere containing sodium hydride (2.54 g, 60% dispersion in mineral oil, 63.5 mmol) was added anhydrous pentane (20 mL). The slurry was allowed to stir for 5 min, allowed to settle, most of the pentane was removed, and anhydrous THF (40 mL) was added. To this suspension was added a solution of methyl 3-hydroxyphenylacetate (9.99 g, 60.1 mmol) in anhydrous THF (20 mL) and the reaction was allowed to stir at room temperature for 20 min. To this mixture was then added a solution of N-phenyltrifluoromethanesulfonimide (22.53 g, 63.1 mmol)) in

anhydrous THF (40 mL) and the reaction was allowed to stir at room temperature until TLC analysis indicated the complete consumption of starting material (1.5 h). The reaction was quenched by the addition of H_2O (10 mL), concentrated to one half original volume, then diluted with $CHCl_3$ (200 mL) and washed with H_2O. The aqueous layer was washed with fresh $CHCl_3$ (50 mL), the combined organic layers were washed with 10% Na_2CO_3, water, and saturated brine, then dried ($MgSO_4$), filtered and concentrated. Column chromatography of the residue (silica gel, 5:95 EtOAc: hexanes, then 10:90 EtOAc: hexanes) gave 17.47 g of the title compound. ^1H NMR (400 MHz, $CDCl_3$) 7.42 (m, 1H), 7.31-7.19 (m, 3H), 3.72 (s, 3H), 3.68 (s, 2H).

b) methyl 3-(2-pyridyl)phenylacetate

To a solution of the compound of Example 3(a) (6.86 g, 23.0 mmol) in anhydrous dioxane (100 mL) was added 2-pyridyltributylstannane (8.89 g, 24.1 mmol), LiCl (2.94 g, 69.3 mmol), 2,6-di-*tert*-butyl-4-methylphenol (a few crystals), and $Pd(PPh_3)_4$ (632.1 mg, 0.55 mmol). The reaction was protected from light with foil and heated at reflux overnight. The reaction was allowed to cool to room temperature and was concentrated. Column chromatography of the residue (silica gel, 1:3 EtOAc: hexanes, then 1:2 EtOAc: hexanes) gave 3.85 g of the title compound. MS (ESI): 228.1 $(M+H)^+$.

c) 3-(2-pyridyl)phenylacetic acid

To a solution of the compound of Example 3(b) (3.8 g, 16.7 mmol) in THF (50 mL) was added a solution of $LiOH \cdot H_2O$ (780.2 mg, 18.6 mmol) in water (10 mL). The reaction was allowed to at room temperature until TLC analysis indicated the complete consumption of starting material (2 h). The reaction mixture was concentrated to remove THF, then neutralized to pH 7 by the addition of 1N HCl, diluted with brine (50 mL), and washed with $CHCl_3$ (100 mL) The aqueous layer was readjusted back to pH 7 by the addition on 1N NaOH and washed with fresh $CHCl_3$ (100 mL). After repeating this procedure once more, the organic layers were combined, dried ($MgSO_4$), filtered and concentrated to give 3.79 g of the title compound. MS (ESI): 214.3 $(M+H)^+$.

d) ((S)-3-methyl-1{3-hydroxy-1-[2-(3-pyridin-2-yl-phenyl)-ethanoyl]-azepan-4-ylcarbamoyl}-butyl)-carbamic acid *tert*-butyl ester

To a solution of the compound of Example 1(g) (0.5g, 1.46 mmol) in CH_2Cl_2 was added EDC (307 mg, 1.60 mmol), HOBt (216 mg, 1.60 mmol) the compound of Example 3(c) (341 mg, 1.60 mmol). The reaction was stirred at room temperature until complete as determined by TLC analysis. Workup and column chromatography (2% methanol:dichloromethane) provided the title compound. MS (ESI): 539 ($M+H^+$).

e) ethyl 5-hydroxybenzofuran-2-carboxylate

To a mixture of aluminum chloride (6.3 g, 47.7 mmol) and ethanethiol (4.5 g, 72.9 mmol) in dichloromethane (81 mL) at 0 °C was added ethyl 5-methoxybenzofuran-2-carboxylate (3.0 g, 13.6 mmol). After stirring for 16h at room temperature, the mixture was poured into water, acidified with 3N HCl and extracted with dichloromethane (2x). The organic layers were combined, washed with saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a white solid (2.16 g, 77%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.08 (m, 1H), 7.02 (m, 1H), 5.35 (s b, 1H), 4.44 (q, 2H), 1.42 (t, 3H).

f) ethyl 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylate

To a solution of the compound of Example 3(e) (0.200 g 0.971 mmol), 4-(2-hydroxyethyl)morpholine (0.165 g, 1.26 mmol), and triphenylphosphine (0.331 g, 1.26 mmol) in THF (4 mL) at 0 °C was added dropwise diisopropylazodicarboxylate (0.254 g, 1.26 mmol). After stirring at room temperature for 16h, the solution was concentrated and purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a white solid (0.235 g, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.07 (m, 2H), 4.43 (q, 2H), 4.14 (m, 2H), 3.76 (m, 4H), 2.86 (m, 2H), 2.61 (m, 4H), 1.40 (t, 3H).

g) 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid

To a stirring solution of the compound of Example 3(f) (0.235 g, 0.74 mmol) in THF (4.0 mL) and water (4.0 mL) was added lithium hydroxide monohydrate (0.035 g, 0.81 mmol). After stirring at reflux for 16h, the solution was concentrated and the residue

was dissolved in water and acidified with 1eq 1N HCl. The mixture was frozen and placed on a lyophilizer for 16h to yield the title compound as an off-white solid (0.150 g, 70%). MS (ESI): 292.1 $(M+H)^+$.

h) 5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid ((S)-3-methyl-1-{3-oxo-1-[2-(3-pyridin-2-yl-phenyl)acetyl]-azepan-4-ylcarbamoyl}-butyl)amide

Following the procedure of Example 1(i)-1(k), except substituting ((S)-3-methyl-1{3-hydroxy-1-[2-(3-pyridin-2-yl-phenyl)-ethanoyl]-azepan-4-ylcarbamoyl}-butyl)-carbamic acid *tert*-butyl ester for [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (i) and 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 710.3 $(M+H^+)$.

Example 4

Preparation of 5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid ((S)-3-methyl-1-{3-oxo-1-[2-(3-pyridin-2-yl-phenyl)acetyl]-azepan-4-ylcarbamoyl}-butyl)amide

The title compound was isolated as the second eluting compound from the HPLC purification in Example 3(h). MS (ESI): 710.3 $(M+H^+)$.

Example 5

Preparation of 4-((S)-4-Methyl-2-{[5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-carbonyl]amino}-pentanoylamino)-3-oxo-azepane-1-carboxylic acid phenylamide

a) [(S)-1-(3-hydroxy-1-phenylcarbamoyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester

To a solution of the compound of Example 1(g) (0.5 g, 1.46 mmol) in dichloromethane (20 mL) was added phenyl isocyanate (0.24 mL, 2.18 mmol). The reaction was stirred at room temperature until complete as determined by TLC analysis. Workup and column chromatography (5% methanol:dichloromethane) provided 578 mg of the title compound. MS (ESI): 463 $(M+H^+)$.

b) 4-((S)-4-methyl-2-{[5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-carbonyl]amino}-pentanoylamino)-3-oxo-azepane-1-carboxylic acid phenylamide

Following the procedure of Example 1(i)-1(k), except substituting [(S)-1-(3-Hydroxy-1-phenylcarbamoyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester for [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (i) and 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 634 ($M+H^+$).

Example 6

Preparation of 5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide

a) [(S)-1-(3-hydroxy-1-phenylsulfonyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester

To a solution of the compound of Example 1(g) (0.5 g, 1.46 mmol) in dichloromethane was added triethylamine (0.4 mL, 2.92 mmol) followed by benzenesulfonyl chloride (0.28 mL, 2.18 mmol). The reaction was stirred at room temperature until complete as determined by TLC analysis. Workup and column chromatography (10% methanol:dichloromethane) provided 450 mg of the title compound. MS (ESI): 484 ($M+H^+$).

b) 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide

Following the procedure of Example 1(i)-1(k), except substituting [(S)-1-(3-hydroxy-1-phenylsulfonyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester for [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (i), and 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 655 ($M+H^+$).

Example 7

Preparation of 5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide

The title compound was isolated as the second eluting compound from the HPLC purification in Example 6(b). MS (ESI): 655 ($M+H^+$).

Example 8

Preparation of 5-(2-Pyrrolidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide

Following the procedure of Example 6(a)-6(b), except substituting 5-(2- pyrrolidin-1-yl-ethoxy)benzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 639 ($M+H^+$).

Example 9

Preparation of 5-(2-Piperidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide

Following the procedure of Example 6(a)-6(b), except substituting 5-(2- piperidin-1-yl-ethoxy)benzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 653 ($M+H^+$).

Example 10

Preparation of Naphthlene-2-carboxylic acid ((S)-3-methyl-1-{3-oxo-1-[2-(3-pyridin-2-yl-phenyl)ethyl]-azepan-4-ylcarbamoyl}-butyl)amide

Following the procedure of Example 1(a)-1(k), except substituting 5-(2- piperidin-1-yl-ethoxy)benzofuran-2-carboxylic acid for benzaldehyde in step (h), and naphthalene-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 557 ($M+H^+$).

Example 11

Preparation of 1H-Indole-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide

Following the procedure of Example 6(a)-6(b), except substituting indole-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 525 ($M+H^+$).

Example 12

Preparation of Benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide

Following the procedure of Example 6(a)-6(b), except substituting benzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. ^1H NMR ($CDCl_3$): δ 1.0 (m, 6H), 1.5-2.1 (m, 5H), 2.2 (m, 2H), 2.6 (m, 1H), 3.5 (d, 1H). 4.1 (m, 1H), 4.7 (m, 2H), 5.0 (m, 1H), 7.2-7.2 (m, 10H).

Example 13

Preparation of 5-(2-Pyrrolidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide

The title compound was isolated as the second eluting compound from the HPLC purification in Example 8. MS (ESI): 639 ($M+H^+$).

Example 14

Preparation of 5-(2-Piperidin-1-yl-ethoxy)-benzofuran-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 9. MS (ESI): 653 ($M+H^+$).

Example 15

Preparation of 5-(2-Morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(4-methyl-pentanoyl)-3-oxo-azepan-4-ylcarbamoyl]-buyl}-amide

Following the procedure of Example 3(a)-3(h), except substituting isocaproic acid for 3-(2-Pyridyl)phenylacetic acid in step (d), the title compound was prepared. MS (ESI): 613 ($M+H^+$).

Example 16

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid

for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 527 ($M+H^+$).

Example 17

Preparation of Naphthalene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and naphthalne-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 537 ($M+H^+$).

Example 18

Preparation of 5-(2-Morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a), the title compound was prepared. MS (ESI): 656 ($M+H^+$).

Example 19

Preparation of 5-(2-Morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 18. MS (ESI): 656 ($M+H^+$).

Example 20

Preparation of 5-(2-Morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the second eluting compound from the HPLC purification in Example 18. MS (ESI): 656 ($M+H^+$).

Example 21

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 16. MS (ESI): 527 ($M+H^+$).

Example 22

Preparation of 4-[2-(2-{(S)-3-Methyl-1-[3-oxo-1-(pvidine-2-sulfonvl)-azepan-4-ylcarbamoyl]-butylcarbamoyl}-benzofuran-5-yloxy)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 4-[2-(2-carboxy-benzofuran-5-yloxy)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 757 ($M+H^+$).

Example 23

Preparation of 5-(2-Piperizin-1-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-butyl}-amide

The compound of Example 22 (0.02 g) was dissolved in 4M HCl in dioxane. The reaction was stirred until complete whereupon it was concentrated to provide the title compound. MS (ESI): 655 ($M+H^+$).

Example 24

Preparation of Quinoline-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and quinoline-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 538 ($M+H^+$).

Example 25

Preparation of Quinoline-6-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and quinoline-6-carboxylic acid *tert*-butyl ester for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 538 ($M+H^+$).

Example 26

Preparation of Quinoline-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and quinoline-4-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 538 ($M+H^+$).

Example 27

Preparation of Quinoline-3-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and quinoline-3-carboxylic acid *tert*-butyl ester for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 538 ($M+H^+$).

Example 28

Preparation of Isoquinoline-3-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and isoquinoline-3-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 538 ($M+H^+$).

Example 29

Preparation of Isoquinoline-1-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and isoquinoline-1-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 538 ($M+H^+$).

Example 30

Preparation of Quinoxaline-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and quinoxaline-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 539 ($M+H^+$).

Example 31

Preparation of Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzo[b]thiophene-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 545 ($M+H^+$).

Example 32

Preparation of 1H-Indole-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and indole-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 526 ($M+H^+$).

Example 33

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-methoxybenzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 557 ($M+H^+$).

Example 34

Preparation of 5-Bromo-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-bromofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 555 ($M+H^+$).

Example 35

Preparation of 5-Nitro-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-nitrofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 522 ($M+H^+$).

Example 36

Preparation of 5-(4-Nitro-phenyl)-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-(4-nitrophenyl)furan-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 598 ($M+H^+$).

Example 37

Preparation of (S)-2-[2-(4-Fluoro-phenoxy)-acetylamino]-4-methyl-pentanoic acid [3-oxo-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 2-(4-fluorophenoxy)acetic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 535 ($M+H^+$).

Example 38

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting thiophene-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 532 ($M+H^+$).

Example 39

Preparation of 5,6-Dimethoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-methyl-1H-imidazole-4-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

a) 2-hydroxy-4,5-dimethoxybenzaldehyde

To a stirring solution of 2-benzyloxy-4,5-dimethoxybenzaldehyde (1.0 g, 3.67 mmol) in ethyl acetate (25 mL) was added 10% palladium on carbon (0.50 g). The mixture was stirred under a hydrogen atmosphere for 4h, then filtered through Celite. The filtrate was concentrated to yield the title compound as a pale yellow solid (0.632 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 11.41 (s, 1H), 9.72 (s, 1H), 6.89 (s, 1H), 6.48 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H).

b) 4,5-dimethoxy-2-ethoxycarbonylmethoxybenzaldehyde

To a stirring solution of the compound of Example 39(a) (0.628 g, 3.4 mmol), and ethyl bromoacetate (0.575 g, 3.4 mmol) in acetone (150 mL) was added K_2CO_3 (0.715 g, 5.2 mmol). After stirring at reflux for 4h, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a colorless oil (0.758 g, 82%). ^1H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.30 (s, 1H), 6.41 (s, 1H), 4.72 (s, 2H), 4.22 (q, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 1.26 (t, 3H).

c) ethyl 5,6-dimethoxybenzofuran-2-carboxylate

A mixture of the compound of Example 39(b) (0.758 g, 2.8 mmol) and potassium carbonate (0.975 g, 7.1 mmol) was stirred at 80 °C in DMF (20 mL) for 5h. The mixture was cooled and partitioned between ethyl acetate and water. The organic layer was washed with water and satruated brine then dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a white solid (0.405 g, 58%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.10 (s, 1H), 7.04 (s, 1H), 4.41 (q, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 1.41 (t, 3H).

d) 5,6-dimethoxybenzofuran-2-carboxylic acid

Following the procedure of Example 3(g), except substituting ethyl 5,6-dimethoxybenzofuran-2-carboxylate for ethyl 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylate, the title compound was prepared as a white solid (0.263 g, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.03 (s, 1H), 7.01 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H).

e) 5,6-Dimethoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-methyl-1H-imidazole-4-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-methylimidazole-4-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5,6-dimethoxybenzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 590 ($M+H^+$).

Example 40

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(1-methyl-1H-imidazole-3-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-methylimidazole-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 530 ($M+H^+$).

Example 41

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(1H-imidazole-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting imidazole-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 516 ($M+H^+$).

Example 42

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(1-methyl-1H-imidazole-4-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-methylimidazole-4-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 530 ($M+H^+$).

Example 43

Preparation of 5-(4-Oxy-morpholino-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

To a solution of the compound of Example 18 (0.01 g) in dichloromethane (2 mL) was added m-CPBA (0.008 g). The reaction was stirred overnight. Workup and column chromatography (30% methanol:dichloromethane) provided the title compound. MS (ESI): 671 ($M+H^+$).

Example 44

Preparation of 5-Hydroxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(1-methyl-1H-imidazole-4-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-methylimidazole-4-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-hydroxybenzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 546 ($M+H^+$).

Example 45

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)]-3-methyl-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 542 ($M+H^+$).

Example 46

Preparation of Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzo[b]thiophene-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 558 ($M+H^+$).

Example 47

Preparation of 5-Bromo-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-bromofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 572 ($M+H^+$).

Example 48

Preparation of 5,6-Dimethoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5,6-dimethoxybenzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 602 ($M+H^+$).

Example 49

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)]-3-methyl-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 45. MS (ESI): 542 ($M+H^+$).

Example 50

Preparation of 5-Bromo-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 47. MS (ESI): 572 ($M+H^+$).

Example 51

Preparation of Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 46. MS (ESI): 558 ($M+H^+$).

Example 52

Preparation of 5,6-Dimethoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 48. MS (ESI): 602 ($M+H^+$).

Example 53

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-methoxybenzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 573 ($M+H^+$).

Example 54

Preparation of 1H-Indole-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and indole-5-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 542 ($M+H^+$).

Example 55

Preparation of Benzo[1,3]dioxole-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzo[1,3]dioxole-5-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 547 ($M+H^+$).

Example 56

Preparation of 5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-(1-oxy-pyridine2-sulfonyl)-azepan-4-ylcarbamoyl]- -buty}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a), the title compound was prepared. MS (ESI): 672 ($M+H^+$).

Example 57

Preparation of 3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 3-methylbenzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 557 ($M+H^+$).

Example 58

Preparation of 1H-Indole-6-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and indole-6-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 526 ($M+H^+$).

Example 59

Preparation of Benzo[1,3]dioxole-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and indole-5-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 531 ($M+H^+$).

Example 60

Preparation of 3,4-Dihydro-2H-benzo[b][1,4]dioxepine-7-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 575 ($M+H^+$).

Example 61

Preparation of 4,5-Dibromo-thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 4,5-dibromothiophene-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 665 ($M+H^+$).

Example 62

Preparation of Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and thieno[3,2-b]thiophene-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 565 ($M+H^+$).

Example 63

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 53. MS (ESI): 573 ($M+H^+$).

Example 64

Preparation of 1H-Indole-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 54. MS (ESI): 542 ($M+H^+$).

Example 65

Preparation of 5-(4-Chloro-phenyl)-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-(4-chloro-phenyl)-furan-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 587 ($M+H^+$).

Example 66

Preparation of 5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-(3-trifluoromethyl-phenyl)-

furan-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 621 ($M+H^+$).

Example 67

Preparation of Benzo[1,3]dioxole-5-carboxylic acid {(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3methyl-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 4-fluorobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a), the title compound was prepared. MS (ESI): 548 ($M+H^+$).

Example 68

Preparation of 5-Bromo-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 34. MS (ESI): 555 ($M+H^+$).

Example 69

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 33. MS (ESI): 557 ($M+H^+$).

Example 70

Preparation of 3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 3-methylbenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 541 ($M+H^+$).

Example 71

Preparation of Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and thieno[3,2-b]thiophene-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 549 ($M+H^+$).

Example 72

Preparation of 2-Phenyl-5-trifluoromethyl-oxazole-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 2-Phenyl-5-trifluoromethyl-oxazole-4-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 622 ($M+H^+$).

Example 73

Preparation of Benzo[1,3]dioxole-5-carboxylic acid {(S)-1-[1-(4-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 4-methoxybenzenesulfonyl chloride for benzenesulfonyl chloride in step (a), the title compound was prepared. MS (ESI): 560 ($M+H^+$).

Example 74

Preparation of Benzofuran-2-carboxylic acid {(S)-1-[1-(4-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 4-methoxybenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 556 ($M+H^+$).

Example 75

Preparation of Furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and furan-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 493 ($M+H^+$).

Example 76

Preparation of Benzo[1,3]dioxole-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 55. MS (ESI): 547 ($M+H^+$).

Example 77

Preparation of 4-Fluoro-{(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-carbamoyl]-butyl}-benzamide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 4-fluorobenzoic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 521 ($M+H^+$).

Example 78

Preparation of 3,4-Dihydro-2H-benzo[b][1,4]dioxepine-7-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 60. MS (ESI): 575 ($M+H^+$).

Example 79

Preparation of 5-Methyl-thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-methylthiophene-2-

carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 523 ($M+H^+$).

Example 80

Preparation of (S)-2-(3-Benzyl-ureido)-4-methyl-pentanoic acid [3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

a) (S)-2-amino-4-methyl-pentanoic acid [3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

Following the procedure of Example 6(a) except substituting 2-pyridinesulfonyl chloride for benzenesulfonyl chloride, the title compound was prepared. MS (ESI): 385 ($M+H^+$).

b) (S)-2-(3-Benzyl-ureido)-4-methyl-pentanoic acid [3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

To a solution of the compound of Example 80(a) (0.25 g) in dichloromethane was added triethylamine (0.17 mL) and benzyl isocyanate (0.088g). The reaction was stirred until complete. Workup and column chromatography (5% methanol:dichloromethane) provided the title compound (0.12 g).

c) (S)-2-(3-Benzyl-ureido)-4-methyl-pentanoic acid [3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

Following the procedure of Example 1(k) except substituting (S)-2-(3-Benzyl-ureido)-4-methyl-pentanoic acid [3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide for benzo[1,3]dioxole-5-carboxylic acid [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-amide, the title compound was prepared. MS (ESI): 516 ($M+H^+$).

Example 81

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid [(S)-1-(1-methanesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]-amide

Following the procedure of Example 6(a)-6(b), except substituting methanesulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-methoxybnzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 494 ($M+H^+$).

Example 82

Preparation of Furan-2-carboxylic acid ({(S)-1-[1-(4-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butylcarbamoyl}-methyl)-amide

Following the procedure of Example 6(a)-6(b), except substituting 4-methoxybenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and N-(2-furan-carbonyl)-glycine for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 563 ($M+H^+$).

Example 83

Preparation of Quinoline-2-carboxylic acid {[(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 4-fluorobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and quinoline-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 555 ($M+H^+$).

Example 84

Preparation of 1-Methyl-1H-indole-2-carboxylic acid {[(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 4-fluorobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and 1-methylindole-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 557 ($M+H^+$).

Example 85

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid {[(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 4-fluorobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-methoxybenzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 574 ($M+H^+$).

Example 86

Preparation of Quinoxaline-2-carboxylic acid {[(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 4-fluorobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-quinolxaline-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 556 ($M+H^+$).

Example 87

Preparation of Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzo[b]thiophene-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 543 ($M+H^+$).

Example 88

Preparation of Benzofuran-2-carboxylic acid-{(S)-1-[1-(3-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

a) {(S)-1-[1-(3-chloro-benzenesulfonyl)-3-hydroxy-azepan-4-ylcarbamoyl]-3-methyl-butyl}-carbamic acid *tert*-butyl ester

To a solution of the compound of Example 1(g) (2.50 g, 7.29 mmol) in dichloromethane (100ml) was added P-NMM (4.0 g) and 3-chlorobenzenesulfonyl chloride (1.85 g, 8.75 mmol). After shaking at room temperature overnight, the solution was filtered. The filtrate was concentrated to yield the title compound as white solid (3.13 g, 83.3%). MS (ESI): 539.8 $(M+Na)^+$.

b) (S)-2-amino-4-methyl-pentanoic acid [1-(3-chloro-benzenesulfonyl)-3-hydroxy-azepan-4-yl]-amide

To a stirring solution of the compound of Example 88(a) (1.0 g, 1.93 mmol) in methnol (10 ml) was added HCl (4M in dioxane) (10 ml). After stirring at room temperature for 3 hr the solution was concentrated to provide a white solid. To a solution of the white solid (0.68 g, 1.50 mmol, 78%) in methnol (37 ml) was added $P\text{-}CO_3$ (2.85 g, 2.63 mmol/g). After shaking for 2hr, the solution was filtered and concentrated to yield the title compound as white solid (0.59 g, 1.42 mmol, 95%). MS (ESI): 417.9 $(M+H)^+$.

c) Benzofuran-2-carboxylic acid-{(S)-1-[1-(3-chloro-benzenesulfonyl)-3-hydroxy-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

To a solution of the compound of Example 88(b) (0.14 g, 0.33 mmol) in dichloromethane (20 mL) was added benzofuran-2-carboxylic acid (0.81 g, 0.50 mmol), 1-hydroxybenzotriazole (0.77 g, 0.57 mmol), and P-EDC (0.67 g, 1 mmol/g) in dichloromethane (10 mL). After shaking at room temperature overnight, the solution was treated with trisamine resin (0.45 g, 3.75 mmol/g). After shaking for another 2 hr, the solution was filtered and concentrated to yield the title compound as a white solid (122 mg, 65%). MS (ESI): 562.2 $(M+H)^+$.

d) Benzofuran-2-carboxylic acid-{(S)-1-[1-(3-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

To a stirring solution of the compound of Example 88(c) (122 mg, 0.22 mmol) in dichloromethane (4 mL) was added Dess-Martin reagent (185 mg, 0.44 mmol). After stirring at room temperature for 2 h, solutions of sodium thiosulfate (2 mL of 10% in water) and saturated aqueous sodium bicarbonate (2 mL) were added simultaneously to the solution. The aqueous layer was extracted with dichloromethane (2x). The organic phases were combined, washed with saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by HPLC (Whelk-O1; ethanol/hexanes) to yield the title compound as a white solid (62.7 mg, 52 %). MS (ESI): 560.2 $(M+H)^+$.

Example 89

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(3-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 5-methoxybenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 590 $(M+H^+)$.

Example 90

Preparation of 3-Methyl-benzofuran-2-carboxylic acid-{(S)-1-[1-(3-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 3-methylbenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 574 ($M+H^+$).

Example 91

Preparation of Benzofuran-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 2-fluorobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a), the title compound was prepared. MS (ESI): 544 ($M+H^+$).

Example 92

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 2-fluorobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 5-methoxybenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 574 ($M+H^+$).

Example 93

Preparation of 7-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 2-fluorobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 7-methoxybenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 574 ($M+H^+$).

Example 94

Preparation of 3-methylbenzofuran-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 2-fluorobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 3-methylbenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 558 ($M+H^+$).

Example 95

Preparation of Benzo[b]thiophene-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 2-fluorobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and benzo[b]thiophene-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 560 ($M+H^+$).

Example 96

Preparation of Quinoxaline-2-carboxylic acid-{(S)-1-[1-(2-fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 2-fluorobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and quinoxaline-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 556 ($M+H^+$).

Example 97

Preparation of 3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 70. MS (ESI): 541 ($M+H^+$).

Example 98

Preparation of Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 71. MS (ESI): 549 ($M+H^+$).

Example 99

Preparation of 3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 57. MS (ESI): 557 ($M+H^+$).

Example 100

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(2,2',4-tridueterio)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

To a solution of the compound of Example 16 (0.03 g) in D_2O:CD_3OD (0.4:4 mL) was added triethylamine (0.04 mL). The reaction was heated to reflux for 2 hours whereupon it was concentrated and dried under vacuum. The residue was the redissolved in the same mixture and heated to reflux overnight. The reaction was concentrated and the residue purified by column chromatography (5% methanol:dichloromethane) to provide the title compound (0.02 g). Separation of the diastereomers by HPLC (Whelk-O1; ethanol/hexanes) provided the title compound. MS (ESI): 530 ($M+H^+$).

Example 101

Preparation of Quinoxaline-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and quinoxaline-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 555 ($M+H^+$).

Example 102

Preparation of Benzofuran-2-carboxylic acid {(S)-2-cyclohexyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

a) 4-*tert*-Butoxycarbonylamino-3-hydroxy-azepane-1-carboxylicacid benzyl ester

To a stirring solution of compound of Example 1(e) (1.04 g, 3.92mmol) in THF was added di-*tert*-butyldicarbonate (0.864 g). After stirring at room temperature for 30 minutes, the reaction mixture was diluted with diethylether and extracted with saturated $NaHCO_3$ The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by

silica gel column to give the title compound as a yellow oil (0.963 g, 2.64 mmol, 67%). MS (ESI): 365.0 $(M+H)^+$.

b) (3-Hydroxy-azepan-4-yl)-carbamic acid *tert*-butyl ester

To a solution of compound of Example 102(a) (0.963g, 2.64mmol) in ethyl acetate (16 ml) was added 10% palladium on carbon (500 mg). After stirring the solution at room temperature for 48 hours, the mixture was filtered through celite. The filterate was concentrated to yield the title compound (0.529 g, 2.29 mmol, 87%). MS (ESI): 231.9 $(M+H)^+$.

c) [3-Hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-carbamic acid *tert*-butyl ester

To a solution of the compound of Example 102(b) (0.53, 2.29 mmol) in dichloromethane (20 ml) was added triethylamine (232 mg) and pyridine-2-sulfonyl chloride (410 mg, 2.32 mmol). After stirring at room temperature for 30 minutes, the mixture was washed with saturated $NaHCO_3$ The organic layer was dried, filtered, concentrated and purified on a silica gel column to give the title compound as a solid (0.58 g, 1.57 mmol, 68%). MS (ESI): 373.0 $(M+H)^+$.

d) 4-Amino-1-(pryidine-2-sulfonyl)-azepan-3-ol

To a stirring solution of the compound of Example 102(c) (0.583 g, 1.57mmol) in ethyl acetate (0.5 ml) was added HCl (4M in dioxane, 3.9 ml). After stirring the reaction mixture for 30 minutes at room temperature, the mixture was concentrated to yield a white solid. The solid was treated with NaOH and then extracted with ethylacetate. The organic layer was dried, filtered, and concentrated to yield a yellow solid (0.35 g, 1.28 mmol, 81%). MS (ESI): 272.9 $(M+H)^+$.

e) {(S)-1-[3-Hydroxy-1-(pryidine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-meth-butyl}-carbamic acid *tert*-butyl ester

To a solution of the compound of example 102(d) (19 mg, 0.070 mmol) in CH_2Cl_2 was added N- *tert*-butoxycarbonyl-L-cyclohexylalanine (28.5 mg, 0.10 mmol), 1-hydroxybenzotriazole (16.1 mg, 0.12 mmol), and P-EDC (140 mg, 0.14 mmol) in dichloromethane. After shaking at room temperature overnight, the mixture was treated with PS-Trisamine. After shaking for another 2 hours, the mixture was filtered and concentrated to yield the title compound as a solid. MS (ESI): 525.0 $(M+H)^+$.

f) (S)-2-Amino-3-methyl-penatanoic acid [3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

To a stirring solution of the compound of example 102(e) (37 mg, 0.07 mmol) in dicloromethane (0.50 ml) was added HCl (4M in dioxane) (0.165 ml). After stirring at room temperature for 30 minutes, the mixture was concentrated, giving a white solid. The white solid was azeotroped with toluene then treated with MP-carbonate (0.35 mmol) in methanol. After four hours of shaking, the mixture was filtered and concentrated to give the title compound as a solid. MS (ESI): 425.0 $(M+H)^+$.

g) Benzofuran-2-carboxylic acid {(S)-2-methyl-1-[3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

To a solution of the compound of example 102(f) (30 mg, 0.070 mmol) in ichloromethane was added benzofuran-2-carboxylic acid (17.0 mg, 0.106mmol), 1-hydroxybenzotriazole (16.1 mg, 0.12 mmol), and P-EDC (140 mg, 0.14 mmol) in dichloromethane. After shaking at room temperature overnight, the mixture was treated with PS-Trisamine. After shaking for another 2 hours, the mixture was filtered and concentrated to yield the title compound as a solid. MS (ESI): 569.0 $(M+H)^+$.

h) Benzofuran-2-carboxylic acid {(S)-2-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

To a stirring solution of the compound of example 102(g) (40 mg, 0.07 mmol) in dichloromethane (0.5 ml) was added Dess-Martin reagent (45 mg, 0.105 mmol). After stirring for 30 minutes, solutions of sodium thiosulfate (10% in water, 0.50 ml) and saturated aqueous sodium bicarbonate (0.50 ml) were added simultaneously to the reaction. The mixture was then extracted with dichloromethane (2 times). The organic layer was dried, filtered, and concentrated. The residue was purified by HPLC (Whelk-O1; ethanol/hexanes) to yield title compound as a white solid. MS (ESI): 567.0 $(M+H)^+$.

Example 103

Preparation of Benzofuran-2-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-pentyl}-amide

Following the procedure of Example 102(a)-102(h), except substituting N-Boc-norleucine for N-*tert*-butoxycarbonyl-L-cyclohexylalanine in step (e), the title compound was prepared. MS (ESI): 527 ($M+H^+$).

Example 104

Preparation of Benzofuran-2-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide

Following the procedure of Example 102(a)-102(h), except substituting N-*tert*-butoxycarbonyl-L-phenylalanine for N-Boc-cyclohexylalanine in step (e), the title compound was prepared. MS (ESI): 561 ($M+H^+$).

Example 105

Preparation of 2-Phenyl-5-trifluoromethyl-oxazole-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 72. MS (ESI): 622 ($M+H^+$).

Example 106

Preparation of 5-Methyl-2-phenyl-oxazole-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-Methyl-2-phenyloxazole-4-

carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 568 ($M+H^+$).

Example 107

Preparation of 3,4-Dimethoxy-N-{(S)-1-[1-(4-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-benzamide

Following the procedure of Example 6(a)-6(b), except substituting 4-methoxybenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and 3,4-dimethoxybenzoic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 576 ($M+H^+$).

Example 108

Preparation of Benzo[b]thiophene-2-carboxylic acid-{(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-yl carbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 4-fluorobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and benzo[b]thiophene-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 560 ($M+H^+$).

Example 109

Preparation of Benzofuran-2-carboxylic acid-{(S)-1-[1-(4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-yl carbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 4-fluorobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 544 ($M+H^+$).

Example 110

Preparation of N-{(S)-1-[1-(4-Fluoro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl}-3-methyl-butyl}-3,4-dimethoxy-benzamide

Following the procedure of Example 6(a)-6(b), except substituting 4-fluorobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and 3,4-dimethoxybenzoic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 546 ($M+H^+$).

Example 111

Preparation of Benzo[b]thiophene-2-carboxylic acid-{(S)-1-(1-methanesulfonyl-3-oxo-azepan-4-yl carbamoyl)-3-methyl-butyl]-amide

Following the procedure of Example 6(a)-6(b), except substituting methanesulfonyl chloride for benzenesulfonyl chloride in step (a) and benzo[b]thiophene-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 480 ($M+H^+$).

Example 112

Preparation of Benzofuran-2-carboxylic acid-{(S)-1-(1-methanesulfonyl-3-oxo-azepan-4-yl carbamoyl)-3-methyl-butyl]-amide

Following the procedure of Example 6(a)-6(b), except substituting methanesulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 464 ($M+H^+$).

Example 113

Preparation of N-[(S)-1-(1-Methanesulfonyl)-3-oxo-azepan-4-ylcarbamoyl}-3-methyl-butyl}-3,4-dimethoxy-benzamide

Following the procedure of Example 6(a)-6(b), except substituting methanesulfonyl chloride for benzenesulfonyl chloride in step (a) and 3,4-dimethoxybenzoic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 484 ($M+H^+$).

Example 114

Preparation of N-{(S)-1-[1-(2-Cyano-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl}-3-methyl-butyl}-4-methanesulfonyl-benzamide

Following the procedure of Example 6(a)-6(b), except substituting 2-cyanobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and 4-methanesulfonylbenzoic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 589 ($M+H^+$).

Example 115

Preparation of Benzofuran-2-carboxylic acid {(S)-1-[1-(2-cyano-benzenesulfonyl)- 3-oxo-azepan-4-yl carbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 2-cyanobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid for 5-(2-morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 551 ($M+H^+$).

Example 116

Preparation of 5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-(1-oxy-pyridine2-sulfonyl)-azepan-4-ylcarbamoyl]- -buty}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 56. MS (ESI): 672 ($M+H^+$).

Example 117

Preparation of 5-Methyl-2 –phenyl-oxazole-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-Methyl-2-phenyloxazole-4-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 584 ($M+H^+$).

Example 118

Preparation of 6-Methyl-N-{(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-nicotinamide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 6-methylnicotinic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 518 ($M+H^+$).

Example 119

Preparation of 5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-(3-trifluoromethyl-phenyl)-furan-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 637 ($M+H^+$).

Example 120

Preparation of N-{(S)-1-[(1-(2-cyano-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl}-3-methyl-butyl}-3,4-dimethoxy-benzamide

Following the procedure of Example 6(a)-6(b), except substituting 2-cyanobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and 3,4-dimethoxybenzoic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 571 ($M+H^+$).

Example 121

Preparation of 4-Methansulfonyl-N-{(S)-1-[4-fluoro-benzenesulfonyl)-3-oxo-azepan-4-carbamoyl]-3-methyl-butyl-benzamide

Following the procedure of Example 6(a)-6(b), except substituting 4-fluorobenzenesulfonyl chloride for benzenesulfonyl chloride in step (a) and 4-methanesulfonylbenzoic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 582 ($M+H^+$).

Example 122

Preparation of (S)-2-[5-(4-Methoxy-phenyl)-pentanoylamnio]-4-methyl-pentanoic acid [3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-(4-methoxyphenyl)pentanoic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 573 ($M+H^+$).

Example 123

Preparation of (S)-2-[2-(3-Benzyloxy-4-methoxy-phenyl)-acetylamnio]-4-methylpentanoic acid [3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 2-(3-Benzyloxy-4-methoxy-phenyl)acetic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 637 ($M+H^+$).

Example 124

Preparation of 5-Methoxybenzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 88(a)-88(d), except substituting thiazole-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 5-methoxybenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 563 ($M+H^+$).

Example 125

Preparation of 7-Methoxybenzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 88(a)-88(d), except substituting thiazole-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 7-methoxybenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 563 ($M+H^+$).

Example 126

Preparation of 3-Methylbenzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 88(a)-88(d), except substituting thiazole-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 3-methylbenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 547 ($M+H^+$).

Example 127

Preparation of Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 88(a)-88(d), except substituting thiazole-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and benzo[b]thiophene-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 549 ($M+H^+$).

Example 128

Preparation of 1-Methyl-1H-indole-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 88(a)-88(d), except substituting thiazole-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 1-methylindole-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 563 ($M+H^+$).

Example 129

Preparation of Quinoxaline-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 88(a)-88(d), except substituting thiazole-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and quinoxaline-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 545 ($M+H^+$).

Example 130

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(thiazole-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 88(a)-88(d), except substituting thiazole-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a), the title compound was prepared. MS (ESI): 533 ($M+H^+$).

Example 131

Preparation of Benzofuran-2-carboxylic acid {(S)-1-[1-(4-chloro-benzenesulfonyl)- 3-oxo-azepan-4-yl carbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 4-chlorobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a), the title compound was prepared. MS (ESI): 561 ($M+H^+$).

Example 132

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(4-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 4-chlorobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 5-methoxybenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 590 ($M+H^+$).

Example 133

Preparation of 7-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(4-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 4-chlorobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 7-methoxybenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 590 ($M+H^+$).

Example 134

Preparation of 3-Methyl-benzofuran-2-carboxylic acid-{(S)-1-[1-(4-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 4-chlorobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 3-methylbenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 574 ($M+H^+$).

Example 135

Preparation of Benzo[b]thiophene-2-carboxylic acid-{(S)-1-[1-(4-chloro-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 4-chlorobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and benzo[b]thiophene-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 576 ($M+H^+$).

Example 136

Preparation of Benzofuran-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 3-methoxybenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a), the title compound was prepared. MS (ESI): 536 ($M+Na^+$).

Example 137

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 3-methoxy benzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 5-methoxybenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 586 ($M+H^+$).

Example 138

Preparation of 7-Methoxy-benzofuran-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 3-methoxy benzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 7-methoxybenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 586 ($M+H^+$).

Example 139

Preparation of 3-Methyl-benzofuran-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 3-methoxy benzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 3-methylbenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 570 ($M+H^+$).

Example 140

Preparation of Benzo[b]thiophene-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 3-methoxy benzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and benzo[b]thiophene-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 572 ($M+H^+$).

Example 141

Preparation of 1-Methyl-1H-indole-2-carboxylic acid-{(S)-1-[1-(3-methoxy-benzenesulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 3-methoxy benzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 1-methylindole-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 569 ($M+H^+$).

Example 142

Preparation of Benzofuran-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting thiophene-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a), the title compound was prepared. MS (ESI): 532 ($M+H^+$).

Example 143

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting thiophene-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 5-methoxybenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 562 ($M+H^+$).

Example 144

Preparation of 7-Methoxy-benzofuran-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting thiophene-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 7-methoxybenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 562 ($M+H^+$).

Example 145

Preparation of 3-Methyl-benzofuran-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting thiophene-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 3-methylbenzofuran-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 546 ($M+H^+$).

Example 146

Preparation of Benzo[b]thiophene-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting thiophene-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and benzo[b]thiophene-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 548 ($M+H^+$).

Example 147

Preparation of Quinoxaline-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting thiophene-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and quinoxaline-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 544 ($M+H^+$).

Example 148

Preparation of 1-Methyl-1-H-indole-2-carboxylic acid-{(S)-3-methyl-1-[3-oxo-1-(thiophene-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting thiophene-2-sulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a) and 1-methylindole-2-carboxylic acid for benzofuran-2-carboxylic acid in step (c), the title compound was prepared. MS (ESI): 545 ($M+H^+$).

Example 149

Preparation of 5,6-Difluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5,6-difluorobenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 562 ($M+H^+$).

Example 150

Preparation of 5,6-Difluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 149. MS (ESI): 562 ($M+H^+$).

Example 151

Preparation of Quinoline-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 24. MS (ESI): 538 ($M+H^+$).

Example 152

Preparation of Quinoline-6-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 25. MS (ESI): 538 ($M+H^+$).

Example 153

Preparation of Quinoline-4-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 26. MS (ESI): 538 ($M+H^+$).

Example 154

Preparation of Isoquinoline-1-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 29. MS (ESI): 538 ($M+H^+$).

Example 155

Preparation of Naphthalene-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 17. MS (ESI): 537 ($M+H^+$).

Example 156

Preparation of Quinoline-3-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 27. MS (ESI): 538 ($M+H^+$).

Example 157

Preparation of 5,6-Dimethoxy-benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[1-(6-methyl-pyridine-2-sulfonyl)3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5,6-dimethoxybenzo[b]thiophene-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 603 ($M+H^+$).

Example 158

Preparation of (R)-1-Benzyl-5-oxo-pyrrolidine-2-carboxylic acid {(S)-3-methyl-1-{3-oxo-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and (R)-1-benzyl-5-oxo-pyrrolidine-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 584 ($M+H^+$).

Example 159

Preparation of Benzofuran-2-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)-ethyl]-amide

Following the procedure of Example 102(a)-102(h), except substituting N-*tert*-butoxycarbonyl-L-2-naphthylalanine for N-Boc-cyclohexylalanine in step (e), the title compound was prepared. MS (ESI): 611 ($M+H^+$).

Example 160

Preparation of Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[1-(3-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 3-methylpyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and thieno[3,2-b]thiophene-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 563 ($M+H^+$).

Example 161

Preparation of 3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(3-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 3-methylpyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 3-methylbenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 555 ($M+H^+$).

Example 162

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(3-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 3-methylpyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-methoxybenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 571 ($M+H^+$).

Example 163

Preparation of 5,6-Difluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5,6-difluorobenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 579 ($M+H^+$).

Example 164

Preparation of 7-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(6-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 7-methoxybenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 557 ($M+H^+$).

Example 165

Preparation of 5,6-Dimethoxy-benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[1-(6-methyl-pyridine-2-sulfonyl)3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 157. MS (ESI): 603 ($M+H^+$).

Example 166

Preparation of 5-Fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-fluorobenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 545 ($M+H^+$).

Example 167

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

a) [(S)-1-(3-hydroxy-6-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester

Following the procedure of Example 1(a)-1(g), except substituting 5-bromo-4-methyl-1-pentene for 5-bromo-1-pentene in step (a), the title compound was prepared. MS (ESI): 358 ($M+H^+$).

b) Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-6-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and benzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 541 ($M+H^+$).

Example 168

Preparation of 5-Fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 166. MS (ESI): 545 ($M+H^+$).

Example 169

Preparation of 5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid{(S)-2-cyclohexyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

a) [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-2-cyclohexyl-ethyl]-carbamic acid *tert* butyl ester

Following the procedure of Example 1(a)-1(g), except substituting N-*tert*-butoxycarbonyl-L-cyclohexylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (f), the title compound was prepared. MS (ESI): 384 ($M+H^+$).

b) 5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid{(S)-2-cyclohexyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-2-cyclohexyl-ethyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and 5-(3-trifluoromethyl-phenyl)-furan-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 677 ($M+H^+$).

Example 170

Preparation of 5,6-Dimethoxy-benzofuran-2-carboxylic acid{(S)-2-cyclohexyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-2-cyclohexyl-ethyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and 5,6-dimethoxybenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 643 ($M+H^+$).

Example 171

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(3-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 162. MS (ESI): 571 ($M+H^+$).

Example 172

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(6-methyl-pyridine-2-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}amide

Following the procedure of Example 6(a)-6(b), except substituting 3-methylpyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 541 ($M+H^+$).

Example 173

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 167. MS (ESI): 541 ($M+H^+$).

Example 174

Preparation of Quinoline-8-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)-ethyl]-amide

a) [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-2-(2-naphthyl)-ethyl]-carbamic acid *tert* butyl ester

Following the procedure of Example 1(a)-1(g), except substituting N-*tert*-butoxycarbonyl-L-2-naphthylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (f), the title compound was prepared. MS (ESI): 428 ($M+H^+$).

b) Quinoline-8-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)-ethyl]-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-2-(2-naphthyl)-ethyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and quinoline-8-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 622 ($M+H^+$).

Example 175

Preparation of Naphthalene-1-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)-ethyl]-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-2-(2-naphthyl)-ethyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and naphthalene-1-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 621 ($M+H^+$).

Example 176

Preparation of Quinoline-8-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide

a) [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-2-phenyl-ethyl]-carbamic acid *tert* butyl ester

Following the procedure of Example 1(a)-1(g), except substituting N-*tert*-butoxycarbonyl-L-phenylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (f), the title compound was prepared. MS (ESI): 378 ($M+H^+$).

b) Quinoline-8-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl)-ethyl]-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-2-phenyl-ethyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and quinoline-8-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 572 ($M+H^+$).

Example 177

Preparation of Naphthyridine-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and naphthyridine-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 539 ($M+H^+$).

Example 178

Preparation of Naphthalene-1-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-2-phenyl-ethyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and naphthalene-1-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 571 ($M+H^+$).

Example 179

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[1-(2-methyl-furan-3-sulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 2-methylfuran-3-sulfonyl chloride for benzenesulfonyl chloride in step (a) and benzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 530 ($M+H^+$).

Example 180

Preparation of Quinoline-2-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-2-phenyl-ethyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and quinoline-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 572 ($M+H^+$).

Example 181

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7S)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

a) allyl-(1-methyl-pent-4-enylidene)-amine

Hex-5-en-2-one (9.8 g, 11.6 ml, 100 mmol) was added to a stirred solution of allylamine (8.55 mmol, 11.25 ml, 150 mmol), 4 Angstrom molecular sieves (52 g), and p-toluene sulfonic acid (10 mg) in CH_2Cl_2 (200 ml) and was stirred overnight. The reaction mixture was concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (13 g, 95%). MS (ESI): 137.9 ($M+H^+$).

b) allyl-(1-methyl-pent-4-enyl)-amine

Sodium borohydride (2.7 g, 71 mmol) was added portionwise to a stirred solution of the compound of Example 181(a) (6.5 g, 47 mmol) in MeOH (100 ml) at 0 C. The reaction mixture was stirred for 30 minutes, then warmed to RT. Approximately 90 ml of MeOH was removed from the reaction mixture by rotary evaporation, then the reaction mixture was diluted with ether (200 ml), then extracted with water then brine. The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo* by rotary evaporation to give a pale yellow liquid that was used in the next reaction without further purification (5.2 g, 80%).

c) allyl-(1-methyl-pent-4-enyl)-carbamic acid benzyl ester

Carbobenzyloxy chloride (9.56 g, 8 ml) was added dropwise to a stirred solution of the compound of Example 181(b) (7 g, 50 mmol), triethylamine (5.5 g, 8.0 ml, 57.5 mmol) in CH_2Cl_2 (100 ml) at 0 C. The reaction mixture was warmed to RT, then was stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (100 ml), then was extracted with water, then brine. The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 4% EtOAc/ hexanes) to give the title compound (8.9 g, 65% yield). MS (ESI): 274.2 ($M+H^+$).

d) 2-methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester

The compound of Example 181(c) (1.036 g, 3.8 mmol) was dissolved in CH_2Cl_2 (10 ml) and a stream of argon gas was bubbled into the reaction mixture for 10 minutes. Then bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (Strem Chemicals, Grubbs' catalyst, 22 mg, 0.027 mmol) was added and the reaction mixture was refluxed for 2 h. Additional bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (11 mg, 0.014 mmol) was added and the reaction mixtrue was refluxed for an additional 1.5 hours. The reaction was cooled to RT under argon overnight, then was concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 5% EtOAc/ hexanes) to give the title compound (0.83 g, 89%). MS (ESI): 246.2 ($M+H^+$).

e) (1S,4R,7R)-4-Methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester

m-Chloro-perbenzoic acid (1.05 g, 57-86% pure) was added to a solution of the compound of Example 181(d) (0.83 g, 3.34 mmol) in CH_2Cl_2 at 0 degrees C. The reaction mixture was stirred for half an hour, then was warmed to RT. Additional m-chloro-perbenzoic acid (0.3 g, 57-86% pure) was added and the reaction was stirred 2 h. The reaction mixture was concentrated *in vacuo* by rotary evaporation, then 80 ml of 9:1 hexanes/EtOAc was added and the reaction mixture was filtered. The filtrate was concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 20% EtOAc:hexanes) to give racemic (1S,4R,7S)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (0.44 g, 50%) and the title compound as a racemic mixture of the title compound (0.15 g, 17% yield). MS (ESI): 262.0 ($M+H^+$).

f) (2R,5S,6S)-5-Azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Sodium azide (0.56 g, 8.62 mmol) was added to a solution of the compound of Example 181(e) (0.75 g, 2.87 mmol) and ammonium chloride (0.46 g, 8.62 mmol) in MeOH (5 ml) and H_2O (0.5 ml), then was refluxed for 6 h. The reaction mixture was concentrated *in vacuo* by rotary evaporation, then was diluted with water (5 ml) and extracted with EtOAc (10 ml). The organic layer was then extracted with water, brine, dried with $MgSO_4$, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 20% EtOAc/hexanes) to yield the title compound (0.7g, 80%). MS (ESI): 305.2 ($M+H^+$).

g) (2R,5S,6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Triphenylphosphine (1.94 g, 7.4 mmol) was added to a solution of the compound of Example 181(f) (1. 5 g, 4.93 mmol) in THF (185 ml) and H_2O (0.7 ml), then was heated to 45 degrees C overnight. The reaction mixture was then diluted with toluene (100 ml x 2) and was azeotroped *in vacuo* by rotary evaporation twice. The resxulting oil was dissolved in MeOH and HCl in Et_2O and the resulting salt was collected following filtration and was used in the next reaction without further purification (1.4 g, 90%).

h) (2R,5S,6S)-5-((S)-2- tert -Butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester and (2S,5R,6R)-5-((S)-2- tert -Butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (0.33 g, 1.73 mmol) was added to a solution of Boc-leucine-hydrate (0.43 g, 1.7 mmol), diisopropylethylamine (0.22 g, 0.3 ml, 1.7 mmol), hydroxybenztriazole (0.25 g, 1.85 mmol), and the compound of Example 181(g) (0.5 g, 1.6 mmol) in DMF (10 ml). The reaction was stirred overnight at RT, then was diluted with EtOAc (100 ml), washed with H_2O (3x 50 ml), brine (50 ml), dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 50% EtOAc/hexanes) to yield the title compound (0.78g, 100%). MS (ESI): 492.0 ($M+H^+$).

i) [(S)-1-((3S,4S,7R)-3-Hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester and . [(S)-1-((3R,4R,7S)-3-Hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester

The compound of Example 181(h) (0.77g, 1.57 mmol) was dissolved in EtOAc (27.5 ml), MeOH (5.5 ml). Then 10% Pd/C (0.39 g) was added and the reaction was stirred overnight under a balloon filled with hydrogen gas. The reaction mixture was filtered through Celite, concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (0.56 g). MS (ESI): 358.1 ($M+H^+$).

j) [(S)-1-((3S,4S,7R)-1-Benzenesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester and [(S)-1-((3R,4R,7S)-1-Benzenesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester

2-Pyridine sulfonyl chloride (0.6 g, 3.4 mmol) was added to a solution of the compound of Example 181(i) (1.0 g, 2.8 mmol), N-methyl morpholine (0.45 ml, 4.1 mmol) in CH_2Cl_2 (35 ml) and was stirred at RT overnight. The reaction mixture was diluted with EtOAc (100 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 2.5% MeOH/ CH_2Cl_2) to yield the title compound (0.9g, 64%). MS (ESI): 499.0 ($M+H^+$).

k) (S)-2-Amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide and (S)-2-Amino-4-methyl-pentanoic acid ((3R,4R,7S)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide

HCl in dioxane (4.0 M, 15 ml) was added to a stirred solution of the compound of Example 181(j) (0.9 g, 1.8 mmol) in MeOH (15 ml). The reaction mixture was stirred for 2h at RT, then was concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (0.85 g).

l) Benzofuran-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide and benzofuran-2-carboxylic acid {(S)-1-[(3R,4R,7S)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (0.35 g, 1.85 mmol) was added to a solution of 2-benzofuran-carboxylic acid (0.3 g, 1.85 mmol), the compound of Example 181(k) (0.85 g, 1.8 mmol), diisopropylethylamine (0.48 g, 0.65 ml, 3.7 mmol),

hydroxybenztriazole (0.25 g, 1.85 mmol) in DMF (10 ml) and was stirred at RT overnight. The reaction mixture was then warmed to RT and was stirred overnight. The reaction mixture was diluted with EtOAc (100 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 2.5% MeOH/ CH_2Cl_2) to yield the title compound (0.8g, 82%). MS (ESI): 542.98 ($M+H^+$).

m) Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7S)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Dess-Martin periodinane (1.0 g, 2.36 mmol) was added to a solution of The compound of Example 181(l) (0.8 g, 1.48 mmol) in CH_2Cl_2 (20 ml) and was stirred at RT for 45 minutes. The solution was washed with 10% $NaHCO_3$ and brine. Purification by column chromatography (60% ethyl acetate/ hexanes) followed by HPLC (Whelk-O1; ethanol/hexanes) gave the title compound as a mixture of diasteromers (0.75 g, 94%). MS (ESI): 541 ($M+H^+$).

Example 182

Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the second eluting compound from the HPLC purification in Example 181. MS (ESI): 541 ($M+H^+$).

Example 183

Preparation of Benzofuran-2-carboxylic acid {(S)-1-[-(3-fluoro-benzensulfonyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-1-butyl}-amide

Following the procedure of Example 88(a)-88(d), except substituting 3-fluoobenzenesulfonyl chloride for 3-chlorobenzenesulfonyl chloride in step (a), the title compound was prepared. MS (ESI): 543 ($M+H^+$).

Example 184

Preparation of Naphthalene-1-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and naphthalene-1-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 537 ($M+H^+$).

Example 185

Preparation of Quinoline-5-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and quinoline-5-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 538 ($M+H^+$).

Example 186

Preparation of 5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid ((S)-3-methyl-1-{3-oxo-1-[1-(1-oxy-pyridin-2-yl)-methanoyl]-azepan-4-ylcarbamoyl}-butyl)-amide

Following the procedure of Example 3(d) and 3(h), except substituting 1-oxypicolinic acid for 3-(2-pyridyl)phenylacetic acid in step (d) and 5-(3-trifluoromethyl-phenyl)-furan-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 601 ($M+H^+$).

Example 187

Preparation of Quinoline-8-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 174. MS (ESI): 622 ($M+H^+$).

Example 188

Preparation of Naphthalene-1-carboxylic acid {(S)-2-naphthalen-2-yl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 175. MS (ESI): 621 ($M+H^+$).

Example 189

Preparation of Quinoline-8-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 176. MS (ESI): 572 ($M+H^+$).

Example 190

Preparation of Naphthalene-1-carboxylic acid {(S)-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-phenyl-ethyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 178. MS (ESI): 571 ($M+H^+$).

Example 191

Preparation of 5-Fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-fluorobenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 561 ($M+H^+$).

Example 192

Preparation of 5-Fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-fluoro-3-methylbenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 575 ($M+H^+$).

Example 193

Preparation of 6-Fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 6-fluoro-3-methylbenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 575 ($M+H^+$).

Example 194

Preparation of 5-Fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 191. MS (ESI): 561 ($M+H^+$).

Example 195

Preparation of 5-Fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 192. MS (ESI): 575 ($M+H^+$).

Example 196

Preparation of 6-Fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 193. MS (ESI): 575 ($M+H^+$).

Example 197

Preparation of Benzo[b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-6-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and

benzo[b]thiophene-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 557 ($M+H^+$).

Example 198

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-6-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and 5-methoxybenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 571 ($M+H^+$).

Example 199

Preparation of 3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-6-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and 3-methylbenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 555 ($M+H^+$).

Example 200

Preparation of Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting pyridine-2-sulfonyl chloride for benzenesulfonyl chloride and [(S)-1-(3-hydroxy-6-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester for [(S)-1-(3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (a), and thieno[3,2-b]thiophene-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 563 ($M+H^+$).

Example 201

Preparation of 3,5-Dimethyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 3,5-dimethylbenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 571 ($M+H^+$).

Example 202

Preparation of 3-Ethyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 3-ethylbenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 571 ($M+H^+$).

Example 203

Preparation of 4-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 4-methoxy-3-methylbenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 587 ($M+H^+$).

Example 204

Preparation of 6-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 6-methoxy-3-methylbenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 587 ($M+H^+$).

Example 205

Preparation of 5-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 5-methoxy-3-methylbenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 587 ($M+H^+$).

Example 206

Preparation of 3,5-Dimethyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 201. MS (ESI): 571 ($M+H^+$).

Example 207

Preparation of 3-Ethyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 202. MS (ESI): 571 ($M+H^+$).

Example 208

Preparation of 4-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 203. MS (ESI): 587 ($M+H^+$).

Example 209

Preparation of 4-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the second eluting compound from the HPLC purification in Example 203. MS (ESI): 587 ($M+H^+$).

Example 210

Preparation of 1-methyl-naphtho[2,1-b]-furan-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 6(a)-6(b), except substituting 1-oxypyridine-2-sulfonyl chloride for benzenesulfonyl chloride in step (a) and 1-methyl-naphtho[2,1-b]-furan-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (b), the title compound was prepared. MS (ESI): 607 ($M+H^+$).

Example 211

Preparation of 6-Methoxy-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

The title compound was isolated as the first eluting compound from the HPLC purification in Example 204. MS (ESI): 587 ($M+H^+$).

Example 212

Preparation of Benzofuran-2-carboxylic acid [(S)-3-methyl-1-[3-oxo-1-quinolin-2-ylmethyl-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 1(a)-1(k), except substituting quinoline-2-carboxaldehyde for benzaldehyde in step (h) and benzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 527 ($M+H^+$).

Example 213

Preparation of 3-Methyl-benzofuran-2-carboxylic acid [(S)-3-methyl-1-[3-oxo-1-quinolin-2-ylmethyl-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 1(a)-1(k), except substituting quinoline-2-carboxaldehyde for benzaldehyde in step (h) and 3-methylbenzofura-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 541 ($M+H^+$).

Example 214

Preparation of Benzo[b]thiophene-2-carboxylic acid [(S)-3-methyl-1-[3-oxo-1-quinolin-2-ylmethyl-azepan-4-ylcarbamoyl]-butyl}-amide

Following the procedure of Example 1(a)-1(k), except substituting quinoline-2-carboxaldehyde for benzaldehyde in step (h) and benzo[b]thiophene-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 543 ($M+H^+$).

Example 215

Preparation of Benzo[b]thiophene-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

a) [(S)-1-(3-hydroxy-1-(2-fluorophenylcarbamoyl)-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester

Following the procedure of Example 5(a), except subsituting 2-fluorophenyl isocyanate for phenyl isocyanate, the title compound was prepared. MS (ESI): 482 ($M+H^+$).

b) Benzo[b]thiophene-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 1(i)-1(k), except substituting [(S)-1-(3-hydroxy-1-(2-fluorophenylcarbamoyl)-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester for [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (i) and benzo[b]thiophene-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 539 ($M+H^+$).

Example 216

Preparation of 3-Methyl-benzofuran-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 1(i)-1(k), except substituting [(S)-1-(3-hydroxy-1-(2-fluorophenylcarbamoyl)-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester for [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (i) and 3-methylbenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 537 ($M+H^+$).

Example 217

Preparation of Quinoxaline-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 1(i)-1(k), except substituting [(S)-1-(3-hydroxy-1-(2-fluorophenylcarbamoyl)-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester for [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (i) and quinoxaline-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 535 ($M+H^+$).

Example 218

Preparation of Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 1(i)-1(k), except substituting [(S)-1-(3-hydroxy-1-(2-fluorophenylcarbamoyl)-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester for [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (i) and thieno[3,2-b]thiophene-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 545 ($M+H^+$).

Example 219

Preparation of Quinoline-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 1(i)-1(k), except substituting [(S)-1-(3-hydroxy-1-(2-fluorophenylcarbamoyl)-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester for [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (i) and quinoline-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 534 ($M+H^+$).

Example 220

Preparation of 4-Methyl-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 1(i)-1(k), except substituting [(S)-1-(3-hydroxy-1-(2-fluorophenylcarbamoyl)-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester for [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (i) and 4-methylthiophene-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 503 ($M+H^+$).

Example 221

Preparation of 5-Methoxy-benzofuran-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 1(i)-1(k), except substituting [(S)-1-(3-hydroxy-1-(2-fluorophenylcarbamoyl)-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester for [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (i) and 5-methoxybenzofuran-2-carboxylic acid for benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 553 ($M+H^+$).

Example 222

Preparation of 4-Methyl-furan-2-carboxylic acid {(S)-1-[1-(2-fluoro-phenylcarbamoyl)-3-oxo-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

Following the procedure of Example 1(i)-1(k), except substituting [(S)-1-(3-hydroxy-1-(2-fluorophenylcarbamoyl)-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester for [(S)-1-(1-benzyl-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert* butyl ester in step (i) and 4-methylfuran-2-carboxylic acid for

benzo[1,3]dioxole-5-carboxylic acid in step (j), the title compound was prepared. MS (ESI): 487 ($M+H^+$).

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.